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REVIEW ARTICLE

Juvenile Dermatomyositis: Advances in Pathogenesis, Assessment, and Management

Alexander K.C. Leung[1,*], Joseph M. Lam[2], Saud Alobaida[3], Kin F. Leong[4] and Alex H.C. Wong[5]

[1]*Department of Pediatrics, The University of Calgary, Alberta Children's Hospital, Calgary, Alberta, Canada;* [2]*Department of Pediatrics and Department of Dermatology and Skin Sciences, The University of British Columbia, Vancouver, British Columbia, Canada;* [3]*Department of Dermatology, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia;* [4]*Pediatric Institute, Kuala Lumpur General Hospital, Kuala Lumpur, Malaysia;* [5]*Department of Family Medicine, The University of Calgary, Calgary, Alberta, Canada*

Abstract: ***Background*:** Juvenile dermatomyositis is the most common inflammatory myopathy in the pediatric age group and a major cause of mortality and morbidity in individuals with childhood rheumatic diseases. Mounting evidence suggests that early diagnosis and timely aggressive treatment are associated with better outcomes.

***Objective*:** The purpose of this article is to provide readers with an update on the evaluation, diagnosis, and the treatment of juvenile dermatomyositis.

***Methods*:** A PubMed search was performed in Clinical Queries using the key term "juvenile dermatomyositis" in the search engine. The search strategy included meta-analyses, randomized controlled trials, clinical trials, observational studies, and reviews. The search was restricted to English literature. The information retrieved from the above search was used in the compilation of the present article.

***Results*:** Juvenile dermatomyositis is a chronic autoimmune inflammatory condition characterized by systemic capillary vasculopathy that primarily affects the skin and muscles with possible involvement of other organs. In 2017, the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) developed diagnostic criteria for juvenile idiopathic inflammatory myopathies and juvenile dermatomyositis. In the absence of muscle biopsies which are infrequently performed in children, scores (in brackets) are assigned to four variables related to muscle weakness, three variables related to skin manifestations, one variable related to other clinical manifestations, and two variables related to laboratory measurements to discriminate idiopathic inflammatory myopathies from non-idiopathic inflammatory myopathies as follows: objective symmetric weakness, usually progressive, of the proximal upper extremities (0.7); objective symmetric weakness, usually progressive, of the proximal lower extremities (0.8); neck flexors relatively weaker than neck extensors (1.9); leg proximal muscles relatively weaker than distal muscles (0.9); heliotrope rash (3.1); Gottron papules (2.1); Gottron sign (3.3); dysphagia or esophageal dysmotility (0.7); the presence of anti-Jo-1 autoantibody (3.9); and elevated serum levels of muscle enzymes (1.3). In the absence of muscle biopsy, a definite diagnosis of idiopathic inflammatory myopathy can be made if the total score is ≥7.5. Patients whose age at onset of symptoms is less than 18 years and who meet the above criteria for idiopathic inflammatory myopathy and have a heliotrope rash, Gottron papules or Gottron sign are deemed to have juvenile dermatomyositis. The mainstay of therapy at the time of diagnosis is a high-dose corticosteroid (oral or intravenous) in combination with methotrexate.

***Conclusion*:** For mild to moderate active muscle disease, early aggressive treatment with high-dose oral prednisone alone or in combination with methotrexate is the cornerstone of management. Pulse intravenous methylprednisolone is often preferred to oral prednisone in more severely affected patients, patients who respond poorly to oral prednisone, and those with gastrointestinal vasculopathy. Other steroid-sparing immunosuppressive agents such as cyclosporine and cyclophosphamide are reserved for patients with contraindications or intolerance to methotrexate and for refractory cases, as the use of these agents is associated with more adverse events. Various biological agents have been used in the treatment of juvenile dermatomyositis. Data on their efficacy are limited, and their use in the treatment of juvenile dermatomyositis is considered investigational.

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*Address correspondence to this author at the Department of Pediatrics, The University of Calgary, Alberta Children's Hospital, Calgary, Alberta, Canada; Tel: (403) 230 3300; Fax: (403) 230 3322; E-mail: aleung@ucalgary.ca

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1. INTRODUCTION

Juvenile dermatomyositis is a chronic autoimmune inflammatory condition characterized by systemic capillary vasculopathy that primarily affects the skin and muscles, although other organs can also be involved [1, 2]. Clinically, the condition is characterized primarily by a heliotrope rash, Gottron papules, an erythematous photosensitive rash on the face, neck and shoulders, and symmetrical proximal muscle weakness [3, 4]. By definition, the onset is prior to 18 years of age. Mounting evidence suggests that early diagnosis and timely aggressive treatment are associated with better outcomes [5-7]. Diagnosis is usually straightforward in patients with typical clinical features but can be challenging otherwise. The purpose of this article is to provide a narrative updated review on the evaluation, diagnosis, and treatment of juvenile dermatomyositis.

2. METHODS

A PubMed search was performed in Clinical Queries using the key term *"*juvenile dermatomyositis*"*. The search strategy included meta-analyses, randomized controlled trials, clinical trials, observational studies, and reviews. The search was restricted to English literature. The information retrieved from the above search was used in the compilation of the present article.

3. EPIDEMIOLOGY

Within the pediatric population, juvenile dermatomyositis is the most common idiopathic inflammatory myopathy, accounting for approximately 85% of cases [8-13]. The reported annual incidence is approximately 3 cases per million children, and the prevalence is approximately 2.5 per 100, 000 children [1, 14, 15]. The disease affects all races and ethnicities. Although some studies showed that the condition is more common in Asian children [16, 17], other studies did not show a racial propensity [2, 18]. By definition, juvenile dermatomyositis affects individuals younger than 18 years of age [19]. The median age of onset is 6.8 years in girls and 7.3 years in boys [2, 19, 20]. The mean time between the onset of the disease and confirmation of the diagnosis is approximately 6 months [21]. Approximately 25% of children are younger than 4 years of age at the onset of the disease [3, 18]. The female-male ratio is approximately 2.3:1 and 5:1 in the United States and the United Kingdom, respectively [22-24].

4. ETIOPATHOGENESIS

While the exact cause is not fully understood, current investigations suggest a genetically determined, aberrant autoimmune response of specific tissue to environmental triggers, with resulting dysfunction and dysregulation of the immune system and tissue inflammation [12, 25, 26]. Autoantibodies are found in the majority of children with juvenile dermatomyositis [7]. It is believed that autoantibodies directed against the endothelium and deposition of immunoglobulins on the endothelial wall lead to the activation of terminal complement components, resulting in vascular injury [21]. Both T and B cells play an important role in the generation of numerous cytokines, notably interleukins (IL) and interferons [21]. The cytokines promote inflammation through paracrine upregulation of endothelial intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 and attraction of other inflammatory cells [12]. This, in turn, may result in endothelial cell swelling, luminal occlusion of capillaries and arterioles, ischemia/infarction of tissue, and perifascicular atrophy [12, 17]. Although inflammation of tissue occurs throughout the body, the skin and the skeletal muscles are most significantly affected [14]. The importance of type 1 interferon is becoming evident [27]. Type 1 interferon, produced by dendritic cells, upregulates genes crucial for immunoregulation and major histocompatibility class (MHC) I expression, activates the cytotoxic effects of natural killer cells, promotes activated T cell survival, stimulates the production of pro-inflammatory cytokines, and supports dendritic cell maturation [11].

Studies have shown that children with juvenile dermatomyositis express antibodies to autoantigens in endothelial cells [28]. In this regard, serum levels of anti-p155/140 antibodies, anti-p140 antibodies, and anti-endothelial cell antibodies are significantly higher in children with juvenile dermatomyositis [29]. There is evidence that interferon plays an important role in the pathogenesis by increasing the expression of interferon-inducible genes in the serum and muscles of children with juvenile dermatomyositis, with the serum levels of these genes correlating with disease activity [30, 31]. MicroRNAs also play a major role in pathogenesis [32]. It has been found that microRNA-193b and microRNA-199b-5p are upregulated whereas microRNA-665 is downregulated in patients with juvenile dermatomyositis [32].

Seasonal or geographical clustering with the onset of juvenile dermatomyositis suggests an environmental trigger. Juvenile dermatomyositis may be triggered by infectious agents (notably coxsackievirus B, enteroviruses, parvovirus B19, Epstein-Barr virus, varicella, and *Streptococcus pyogenes*) and certain immunizations (notably rubella and Bacillus Calmette-Guérin [BCG]) [16, 33, 34]. Children with immunodeficiency are particularly at risk [17].

Other environmental triggers include heavy exposure to ultraviolet radiation, exposure to school chalk dust, tobacco smoking, inhaled air pollutants (*e.g*., traffic generated pollutant carbon monoxide, gasoline vapor), medications (*e.g*., nonsteroidal anti-inflammatory drugs, D-penicillamine), and bone marrow transplants [35-38]. Maternal microchimerism may also play a role as persistent maternal cells are found in the blood of children with juvenile dermatomyositis. Other environmental triggers such as lipid-lowering agents, silica, and silicone implants, which are associated with adult-onset dermatomyositis, have not been described in children [39].

There is a genetic predisposition as children with human leukocyte antigens (HLA)-B*08, HLA-DRB1*0301, HLA-DPB1*0101, HLA-DQA1*0301, HLA-DQAI*0501, HLA-DR3, and HLA-DRB*0301 are particularly susceptible to juvenile dermatomyositis [1, 22]. Non-HLA-associated genes,

such as genetic polymorphisms in interleukin-1 receptor antagonist, tumor necrosis factor-alpha, immunoglobulin gamma heavy chain, immunoglobulin kappa light chain, protein tyrosine phosphatase, chemokine C-C motif ligand 21, phospholipase C-like protein 1, and B lymphoid kinase, are known risk factors [7, 22]. Affected patients are at increased risk for other autoimmune diseases, particularly systemic lupus erythematosus [40].

5. HISTOPATHOLOGY

Histopathological features include atrophy of the perifascicular myocytes, perivascular mononuclear cell infiltrate, degeneration/necrosis of type I and type II muscle fibers, regeneration of muscle fibers with associated basophilia, tubular reticular inclusions, variation in the size of muscle fibers, centralization of nuclei in muscle fibers, damaged mitochondria, reduced number of capillaries, endothelial swelling, obliteration of capillary lumen, CD4+ helper cells, B cells, and macrophages in the perivascular and perimysial areas, endomysial and perimysial fibrosis, and increased expression of MHC class 1 molecules [14, 31, 41].

6. CLINICAL MANIFESTATIONS

Approximately 80% of patients have prominent constitutional symptoms, including malaise, fatigue, asthenia, anorexia, irritability, headache, low-grade fever, and weight loss [17, 42]. The onset of clinical features is usually insidious.

6.1. Cutaneous Manifestations

Cutaneous manifestations are most common and may precede the muscle involvement by months [14]. A heliotrope rash, Gottron papules, and Gottron sign are pathognomonic and are absent in other forms of juvenile idiopathic inflammatory myopathy [14, 17, 43]. The heliotrope rash is the most common initial finding on presentation and consists of symmetrical lilac discoloration or violaceous erythema of the upper eyelids, often with diffuse swelling of the eyelids (Fig. **1**) [1]. Unilateral heliotrope rash has rarely been reported [44]. There may be an accentuation of vasculature along the lash line (eyeliner sign) [12]. Periorbital edema, facial edema and eyelid capillary telangiectasia occur in 50 to 90% of affected children [1]. Rarely, periorbital edema is the initial sign of juvenile dermatomyositis and precedes the appearance of the heliotrope rash [45]. Photosensitive facial and malar erythema may also be present (Fig. **2**). Facial erythema may cross the nasolabial folds in contrast to the malar erythema, which has no nasolabial involvement. Malar erythema is typically seen in patients with systemic lupus erythematosus.

Gottron papules are shiny, erythematous or violaceous, scaly papules that occur symmetrically over the bony prominences, such as the dorsal aspects of distal interphalangeal, proximal interphalangeal, metacarpophalangeal joints and on the extensor surfaces of the knees, ankles and elbows (Fig. **3**) [14, 21]. They are present in 50 to 80% of children with juvenile dermatomyositis [21, 46]. Telangiectasias are often seen within the Gottron papules [14]. Gottron sign refers to erythematous, non-papular lesions in the same distribution of Gottron papules (Fig. **4**) [22]. Gottron papules on the palmer surface (Fig. **5**), referred to as inverse Gottron papules, have rarely been reported [47, 48]. Later in the course of the disease, Gottron papules may become atrophic and appear as hyper- or hypopigmented flat lesions [46].

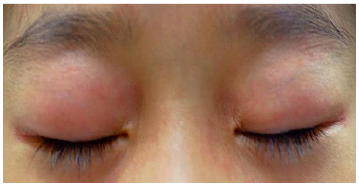

Fig. (1). A characteristic heliotrope rash and edema of the upper eyelids in a 9-year-old girl with juvenile dermatomyositis (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

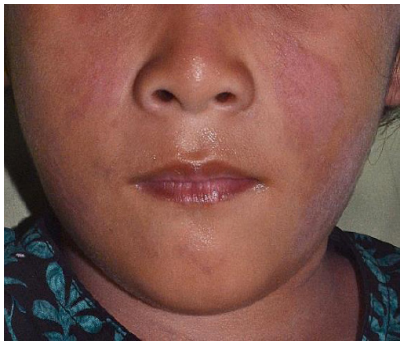

Fig. (2). Facial erythema in a child with juvenile dermatomyositis (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Fig. (3). Gottron papules on the metacarpophalangeal joints and interphalangeal joints in a child with juvenile dermatomyositis (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

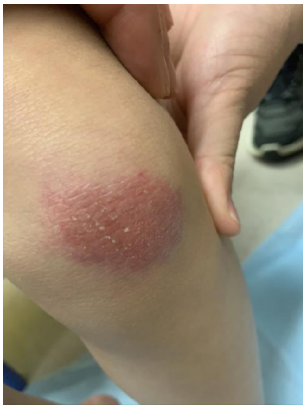

Fig. (4). Gottron sign on the left knee (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Fig. (5). Inverse Gottron papules on the palmar surface of the right hand (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Other typical skin changes include violaceous erythema in a photosensitive distribution on the front of the neck and chest (V-sign) and nape of the neck extending to the shoulders and upper back (shawl sign) [47, 49]. Approximately 50% of patients with juvenile dermatomyositis experience photosensitivity. Both cutaneous and muscular manifestations of the disease are exacerbated by exposure to sunlight [17]. Affected patients may have palmar hyperkeratosis (mechanic's hands), characterized by scaly, hyperkeratotic lesions along the ulnar aspect of thumbs or radial aspect of fingers, notably the index and middle finger [42, 47, 48]. Linear hyperpigmentation and fissuring may also be seen in mechanic's hands [42]. Other less common cutaneous manifestations include seborrheic dermatitis-like dermatitis on the scalp [48]; hypopigmentation in the medial angle of eyes possibly as a result of inflammation at the medial angles of the eyes leading to the hypopigmentation or hyperpigmentation of the entire eyelid with sparing of the medial angles; trachyonychia [50]; and palmar erythema [51, 52]. Koebner phenomenon which is typically observed in psoriasis and lichen planus, and less commonly in cutaneous lupus erythematosus and vitiligo, has also been observed in patients with juvenile dermatomyositis [53-55]. Pruritus is not uncommon and occurs in approximately one-third of children with juvenile dermatomyositis [56].

Nailfold changes include periungual erythema, telangiectasias, capillary occlusion, dilated capillary loops, end-row capillary loops, capillary tortuosity, loss of capillaries (capillary dropout), splinter hemorrhage, and hypertrophic and ragged cuticle (Samitz sign) (Fig. **6**) [22, 47, 57]. These changes can be visualized easily by capillaroscopy, which in turn, can be used to quantitate the number of end row loops [58]. Nailfold changes are present in 68 to 91% of children at the time of diagnosis [12]. It has been shown that a low nailfold capillary density (defined as less than 6 capillaries per mm) is associated with impaired pulmonary function [59]. Infarction of skinfold or digital ulceration indicates a more severe disease.

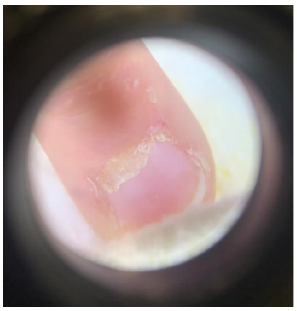

Fig. (6). Cuticle hypertrophy, dilated capillaries and splinter hemorrhages on the proximal nail fold - dermoscopic view (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Calcinosis (soft tissue calcification) or dystrophic calcification, due to abnormal deposition of calcium phosphate, hydroxyapatite, or fluorapatite crystals in the skin, subcutaneous tissue or, less commonly, in the muscle, fascia, and tendons, occurs in approximately one-third of patients with juvenile dermatomyositis [15, 60, 61]. Clinically, calcinosis cutis presents as flesh-colored or white nodules over bony prominences such as digits, elbows, knees, and areas of trauma (Fig. **7**) [12, 18]. The condition most commonly occurs 1 to 3 years after the onset of the disease [18, 57]. Risk factors for the development of calcinosis include young age of onset, delay in diagnosis, delayed or inadequate treatment, use of nonsteroidal immunosuppressive therapy, severe disease, prolonged high disease activity, cardiac involvement, lipodystrophy, joint contractures, presence of autoantibodies against nuclear matrix protein 2, and tumor necrosis factor alpha-308 A genotype [18, 62-64]. Calcinosis cutis is painful and can be cosmetically unsightly if it occurs in visibly exposed areas. It may lead to skin ulceration, skin atrophy, nerve entrapment, and contractures. Subcutaneous involvement such as calcinosis and panniculitis significantly correlates with elevated serum aldolase and long-term morbidity and has an adverse effect on the quality of life [65-67].

Cutaneous vasculitis may take the form of livedo reticularis, urticarial-like lesions, palpable purpura, skin ulcera-

tions, Raynaud phenomenon, alopecia, subcutaneous edema, and skin ulceration [17, 22]. Subcutaneous edema, an indicator of severe disease, is related to inflammatory vasculopathy with resulting partial or complete occlusion of the lumen of small blood vessels [68]. Skin ulceration (Fig. **8**), characterized by circular lesions with sharp margins, occurs in 5 to 30% of children (more frequently in younger children) with juvenile dermatomyositis [18, 69, 70]. Sites of predilection include the digital pulp, extensor surfaces of joints, over the surface of Gottron papules and calcinosis, and axillae [71]. Skin ulceration is most often caused by ischemia of the skin secondary to vasculopathy and, when present, may signal vasculopathy in other organs such as the gastrointestinal tract [12, 22, 69]. Ulceration of the skin is associated with significant pain, increased resistance to immunosuppressive treatment, and a severe disease which can be life-threatening [12, 69, 70]. Skin ulceration may also result from calcinosis cutis [18].

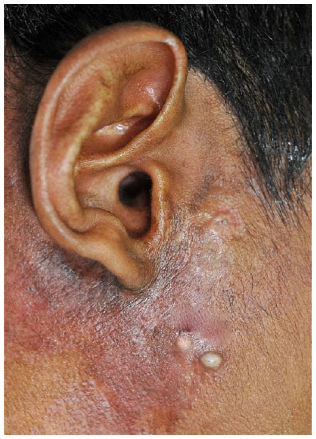

Fig. (7). A 13-year-old boy with calcinosis cutis presenting as two whitish nodules in the right infra-auricular area (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

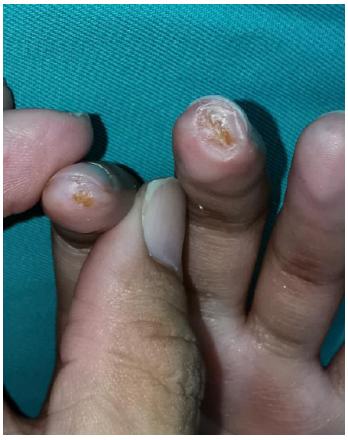

Fig. (8). Crusted ulcers over the tip of the right index and middle finger of a 9-ear-old girl with juvenile dermatomyositis (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

6.2. Musculoskeletal Manifestations

Muscle weakness is a cardinal clinical manifestation of juvenile dermatomyositis. The myopathy primarily affects the proximal muscles such as the neck flexors, shoulder abductors, as well as hip flexors, extensors, and adductors, but can also affect the axial muscles, especially in children [14, 72]. The muscle weakness is generally bilateral, symmetrical, and slowly progressive [15, 72]. Clinically, this is manifested as fatigability, weakness, difficulty in getting up from the floor or chair, climbing stairs, squatting, and lifting arms above the head and for such actions as washing/combing hair or shaving, and reduction in exercise tolerance [17]. A Gower sign (use of hands and arms to "climb up the body" from a sitting or squatting position to attain an upright posture) may be present. Toddlers may present with frequent falls. Myalgia in the affected muscle group commonly occurs but is generally not as intense as that observed in acute myositis [1, 72]. Validated measures of muscle strength at diagnosis and follow-up include the Childhood Myositis Assessment Scale (CMAS) - a measure of muscle strength, Manual Muscle Testing of 8 muscle groups (MMT-8) - a measure of muscle strength and performance, Disease Activity Score (DAS) - a measure of skin and muscle involvement, Myositis Disease Activity Assessment Tool (MDAAT) - a measure of overall disease activity, Childhood Health Assessment Questionnaire (CHAQ) - a measure of physical function, and Juvenile DermatoMyositis Activity Index (JDMAI) - a measure of muscle strength, skin disease activity, overall disease activity, and the child's well-being [73-78]. Validated measures of muscle strength are important outcome measures in clinical trials and form part of the Paediatric Rheumatology International Trials Organization (PRINTO) remission criteria [79, 80]

As the disease progresses, all muscles may become affected. The involvement of distal muscle may affect fine motor movement. If pharyngeal or respiratory muscles are involved, the child may present with dysphagia, coughing or choking with swallowing, nasal speech, dysphonia, and dyspnea [1].

Arthralgia involving the small joints is a common presenting symptom [1]. This may be accompanied by morning stiffness. Larger joints may also be affected. Arthritis, when present, is usually symmetrical, non-erosive, and non-deforming [1].

6.3. Clinical Variants

Approximately 5% of children with juvenile dermatomyositis do not have obvious muscle weakness, a condition referred to as juvenile clinically amyopathic juvenile dermatomyositis [22, 43]. Juvenile clinically amyopathic dermatomyositis comprises juvenile amyopathic dermatomyositis and juvenile hypomyopathic dermatomyositis [43]. Juvenile clinically amyopathic juvenile dermatomyositis comprises juvenile amyopathic dermatomyositis and juvenile hypomyopathic dermatomyositis for at least 6 months who have no proximal muscle weakness or evidence of muscle disease, as defined by normal clinical examination, normal muscle

Table 1. Complications that may result from juvenile dermatomyositis.

A. Musculoskeletal involvement
1. Muscle atrophy [91]
2. Contractures (usually result from myositis leading to fibrosis or calcinosis rather than arthritis) [12, 22, 103]
3. Muscular calcinosis [12]
4. Osteoporosis [91]
B. Gastrointestinal involvement
1. Bowel dysmotility [18]
2. Abdominal pain [85]
3. Malabsorption [85]
4. Mucosal ulceration [85]
5. Gastrointestinal hemorrhage [85]
6. Pneumatosis intestinalis [22]
7. Intestinal perforation [85]
8. Acute acalculous cholecystitis (presumably caused by the vasculitic process) [100]
9. Acute hepatitis [85]
10. Acute pancreatitis [85]
C. Cardiovascular involvement
1. Conduction defects [87, 90]
2. Dysrhythmias [87, 101]
3. Myocarditis/pericarditis [12, 87]
4. Dilated cardiomyopathy [12, 87]
5. Hypertension [12, 87, 101]
6. Systemic capillary leak syndrome (characterized by recurrent episodes of fluid and protein leakage into the interstitial compartment, leading to hypoalbuminemia and hypovolemic shock) [95]
7. Accelerated atherosclerosis [12, 101]
D. Pulmonary involvement
1. Respiratory muscle dysfunction [97]
2. Aspiration pneumonia [97]
2. Pneumomediastinum [89]
2. Interstitial lung disease (uncommon in children; often associated with anti-melanoma differentiation associated gene 5 [MDA5], IL-18, Krebs von den Lungen 6 [KL-6], and anti-tRNA synthetase autoantibodies) [22, 93, 97, 104]
E. Renal involvement
1. Proteinuria [9]
2. IgA nephropathy [9]
3. Renal failure [9]
F. CNS and neurological involvement
1. Neuropsychiatric manifestations (wide mood changes, depression, hallucination)
2. Nerve entrapment (from dystrophic calcification)
3. Seizures [12, 101]
4. Cerebral infarction [12, 101]
G. Ophthalmic involvement
1. Retinal exudates
2. Retinal hemorrhage
3. Chorioretinopathy [88]
4. Neuromyelitis optica [92]
H. Endocrine and metabolic involvement
1. Obesity [101]
2. Growth retardation [91, 96]
3. Pubertal delay [96]
4. Menstrual irregularities [91]
5. Diabetes mellitus [101]
6. Dyslipidemia [94, 101, 105]
7. Lipodystrophy (typically affecting the upper part of the trunk; may be associated with metabolic sequelae syndrome) [101]
I. Miscellaneous
1. Anasarca (resulting from diffuse capillary leak due to damage of the vascular endothelium; a poor prognostic sign)
2. Immune dysregulation (partly due to long-term systemic corticosteroid therapy) [99]
3. Malignancy (notably, lymphoma; very rare in childhood) [86, 91, 98, 102]

enzymes, and normal muscle biopsy [81, 82]. Affected children, however, may develop muscle involvement at a later stage [81]. Juvenile hypomyopathic dermatomyositis simulates juvenile amyopathic dermatomyositis but have subclinical myositis evidenced by elevations of serum muscle enzymes [82]. Generally, children with juvenile amyopathic or hypomyopathic dermatomyositis have fewer or no systematic manifestations or complications (*e.g.*, fatigue, myalgia, calcinosis cutis, interstitial lung disease, other organ involvement, malignancy), less functional disability, and better prognosis [82]. They often have anti-transcription intermediary factor 1-gamma (anti-TIF1-gamma, aka anti-p155/140) autoantibodies [82].

Another variant is dermatomyositis sine dermatitis which is distinguished from classical juvenile dermatomyositis by a lack of skin involvement [83]. Affected patients have symmetric proximal muscle weakness, the elevation of muscle enzymes, electromyographic (EMG) findings suggestive of myopathy and muscle biopsy with characteristic pathological findings of myositis (Nilipour). Dermatomyositis sine dermatitis is significantly associated with anti-nuclear matrix protein 2 (anti-NXP-2) autoantibodies [84].

7. COMPLICATIONS

There are multiple complications that may result from the involvement of other organs. These are listed in Table **1** [12, 18, 22, 85-105]. Most complications are related to the chronicity of the disease. Secondary complications may result from medical treatments such as corticosteroids and disease-modifying anti-rheumatic drugs [106]. Juvenile dermatomyositis imposes a heavy burden on the healthcare system, in terms of cost of medication and cost of care [107]. The disease has a significant impact on the quality of life of the patients and their parents, especially those in the minority race and lower socioeconomic status [108, 109]. It has been shown that families of children with juvenile dermatomyositis are more likely to have communication problems and difficulties in family functioning as well as an increased number of conflicts [108, 110]. Affected children, their siblings and parents are vulnerable to psychological distress [7].

8. LABORATORY FINDINGS

Muscle enzymes assessment such as creatine kinase (CK), aldolase, alanine aminotransferase (ALT/ALAT/SGPT), lactate dehydrogenase (LDH), aspartate aminotransferase (AST/ASAT/SGOT) should be performed as they are often elevated with active myositis [79]. ALT is most commonly elevated on initial presentation. A rise in LDH and AST is most helpful in the detection of a disease flare. Elevated serum levels of muscle enzymes are time-dependent, and they tend to normalize 4 to 5 months after disease onset or flare [31, 110]. The aldolase is most resistant to normalization. The muscle enzymes are elevated in approximately 90% of cases [72]. Muscle enzymes as well as von Willebrand factor antigen, and fibrin degradation product, markers of endothelial cell damage, have been used to monitor disease activity [43].

Laboratory tests that may be useful to rule out alternate diagnoses or to assess for potential complications or organ involvement include complete blood cell count (CBC), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), serum electrolytes, renal function tests, and liver function tests [22, 79]. Antinuclear antibody (ANA) is found in approximately 70% of children with juvenile dermatomyositis [22]. However, a positive ANA test is nonspecific and has limited diagnostic value [22, 79]. A negative ANA test, on the other hand, can help to rule out systemic lupus erythematosus [6]. Other tests that can be used to rule out rheumatic disorders include serum levels of complement 3 (C3), C4, antibodies against extractable nuclear antigens and double-stranded DNA [6].

Testing for myositis-specific antibodies such as antibodies against histidyl-tRNA synthetase (anti-Jo-1), nuclear helicase (anti-Mi-2), melanoma differentiation associated gene 5 (anti-MDA5), small ubiquitin-like modifier activating enzyme (anti-SAE), nuclear matrix protein-2 (anti-NXP2), anti-p155/140 and, to a lesser degree, myositis-associated antibodies such as antibodies against signal recognition particle (anti-SRP) and U1-ribonucleoprotein (anti-U1-RNP) should be considered [79]. These antibodies have diagnostic and prognostic value [112]. The myositis-specific antibodies are found in most children with juvenile dermatomyositis but not in healthy children or children with other autoimmune diseases or muscular dystrophy [12, 27, 113, 114]. Different types of antibodies (anti-p155/140, anti-MJ, anti-MI-2, anti-synthetase, anti-SRP) are associated with specific clinical manifestations, the severity of disease, complications, prognosis, and response to treatment [6, 12, 14, 18, 61]. Testing for myositis-specific antibodies should be considered in children with atypical clinical features and/or unusual clinical course [41]. However, the tests are expensive, not readily available, and are thus not routinely performed.

Characteristic EMG changes include short, small amplitude, polyphasic motor unit action potential, fibrillations, positive sharp waves, insertional irritability, and high-frequency repetitive discharges [41]. Because muscle inflammation is patchy, EMG is not always diagnostic and is normal in approximately 19% of juvenile dermatomyositis cases [19, 111]. Magnetic resonance imaging (MRI) helps to distinguish between affected and unaffected muscles [26, 115]. Quantitation of inflammatory changes in affected muscles has been shown to correlate with disease activity [26, 115]. MRI is a reliable diagnostic tool to assess inflammation in the muscles at the time of diagnosis as well as during follow-up [79]. The classic features seen on MRI include muscle edema, honeycombed appearance of affected muscles, perifascicular edema, and a high T2 signal [14]. A muscle MRI can help in the objective assessment of juvenile dermatomyositis flares [79, 116]. Other advantages of a muscle MRI include its sensitivity to low levels of muscle inflammation and the ability to assess many muscles simultaneously [6, 115]. In addition, MRI is of invaluable aid in the selection of a site for EMG and muscle biopsy [72, 114]. Some investigators use MRI as an alternative diagnostic tool in confirming the diagnosis of juvenile dermatomyositis because the procedure is non-invasive and does not involve ionizing radiation [4, 112, 114]. Muscle biopsies often show a characteristic vasculitis with accompanying degeneration of muscle fibers [14, 111]. The muscle selected for the examination should be affected clinically but not atrophic [17]. A muscle biopsy should be considered especially if the clinical evaluation and laboratory testing are inconclusive [79].

9. DIFFERENTIAL DIAGNOSIS

A heliotrope rash over the upper eyelids and Gottron papules/sign are pathognomonic of juvenile dermatomyositis and are absent in other forms of juvenile idiopathic inflammatory myopathy such as juvenile polymyositis, immune-mediated necrotizing myositis, inclusion body myositis, and myositis associated with connective tissue diseases, such as systemic lupus erythematosus, juvenile rheumatoid arthritis, systemic sclerosis, mixed connective tissue disease, and scleroderma (referred to as overlap syndromes) [6, 11, 81]. A further distinction can be made by specific clinical findings and serologic testing of specific autoantibodies associated with the various connective diseases.

Other causes of muscle weakness should be considered in the differential diagnosis. These include muscular dystrophies (*e.g.*, Duchenne muscular dystrophy, Becker muscular dystrophy, Emery-Dreifuss muscular dystrophy, limb-girdle muscular dystrophy, facioscapulohumeral muscular dystrophy, congenital muscular dystrophy, myotonic muscular dystrophy, oculopharyngeal muscular dystrophy), neuromuscular transmission disorders (*e.g.*, myasthenia gravis, botulism, tick paralysis, spinal muscular atrophy, Gullain-Barré syndrome, poliomyelitis), hereditary motor-sensory neuropathies (*e.g.*, peroneal muscular atrophy, Déjerine-Sottas disease, Refsum disease, Rouddy-Lévy syndrome, giant axonal neuropathy, congenital hypomyelinating neuropathy), endocrine myopathies (*e.g.*, hypothyroidism, hyperthyroidism, hyperparathyroidism, Addison disease, Cushing syndrome, hyperaldosteronism, chronic growth hormone excess), metabolic myopathies (*e.g.*, glycogen storage disease, lipid storage disease, mitochondrial defects, myoadenylate deaminase deficiency, periodic paralysis, vitamin E deficiency myopathy), acute infectious myositis (influenza [typically associated with calf pain], coxsackievirus, echovirus, poliovirus, parvovirus, *Toxoplasma gondii*, *Trichinella spiralis*, *Legionella pneumophilia*) and drug-induced myopathy (*e.g.*, corticosteroids, propylthiouracil, cimetidine, procainamide, chloroquine, hydroxychloroquine) [27, 41]. The absence of the characteristic cutaneous lesions found in juvenile dermatomyositis (such as heliotrope rash, Gottron papules/sign, violaceous erythema in a photosensitive distribution, nailfold capillary changes, calcinosis cutis) and the distinctive features unique in each distinct condition allow a relatively straightforward differentiation from juvenile dermatomyositis.

Drugs such as hydroxyurea, tryptophan, and penicillamine can produce an eruption that may mimic that of juvenile dermatomyositis. A history of drug ingestion and the lack of muscle involvement may give clues for the diagnosis.

Dermatological disorders such as psoriasis, atopic dermatitis, nummular eczema, tinea corporis, and secondary syphilis may present with an erythematous rash with scaling [117-121]. The absence of muscle involvement, heliotrope rash, and Gottron papules/sign help to differentiate these conditions from juvenile dermatomyositis.

10. DIAGNOSIS

Traditionally, the diagnosis of juvenile dermatomyositis is made based on the following 5 criteria proposed by Bohan and Peter [122], namely, characteristic cutaneous changes, consisting of heliotrope dermatitis and Gottron papules; progressive symmetrical weakness of proximal muscles; elevated serum skeletal muscle enzyme levels; myopathic changes on EMG; and evidence of inflammatory myositis on muscle biopsy. According to Bohan and Peter, typical skin findings in combination with 3 other criteria must be fulfilled for a definite diagnosis [122]. The diagnosis is probable if 3 of the 5 criteria are present [122]. However, due to their invasive nature, EMG and muscle biopsy are presently less frequently employed [41]. Also, normal serum levels of muscle enzymes do not exclude juvenile dermatomyositis because the elevation of the muscle enzymes is time-dependent. In an international survey among pediatric rheumatologists in 2006, all respondents used clinical features of juvenile dermatomyositis to make the diagnosis [123]. Elevated serum muscle enzymes, changes in muscle biopsy typical of myositis, and myopathic changes in EMG were used as diagnostic aids in 87, 61, and 56% of cases, respectively [123].

There is less utilization of muscle biopsy nowadays because of the invasiveness of the procedure and concerns that the diagnosis may be missed because of the patchiness of muscle involvement [6]. Many investigators are now substituting muscle biopsy with MRI for both diagnosis and follow-up [124].

In 2017, the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) developed diagnostic criteria for juvenile idiopathic inflammatory myopathies and juvenile dermatomyositis [125, 126]. In the absence of muscle biopsies which are infrequently performed in children, scores (in brackets) are assigned to four variables related to muscle weakness, three variables related to skin manifestations, one variable related to other clinical manifestations, and two variables related to laboratory measurements to discriminate idiopathic inflammatory myopathies from non-idiopathic inflammatory myopathies. The following are the variables and the associated scores: objective symmetric weakness, usually progressive, of the proximal upper extremities (0.7); objective symmetric weakness, usually progressive, of the proximal lower extremities (0.8); neck flexors relatively weaker than neck extensors (1.9); proximal muscles in the legs relatively weaker than distal muscles (0.9); heliotrope rash (3.1); Gottron papules (2.1); Gottron sign (3.3); dysphagia or esophageal dysmotility (0.7); the presence of anti-Jo-1 autoantibody (3.9); and elevated serum levels of CK or ALT/ALAT/SGPT or LDH or AST/ASAT/SGOT (1.3) [125, 126]. In the absence of muscle biopsy, a definite diagnosis of idiopathic inflammatory myopathy can be made if the total score is ≥7.5 (level of probability ≥90%) [41, 125, 126]. The diagnosis is probable if the total score is ≥ 5.5 and <7.5 (level of probability ≥55 to <90%) and the diagnosis is possible if the total score is > 5.3 and < 5.4 (level of probability ≥50 to <55%) [41, 125, 126]. The EULAR/ACR classification criteria for idiopathic inflammatory myopathies have been endorsed by international dermatology, rheumatology, neurology, and pediatric groups [125, 126]. According to the EULAR/ACR classification criteria, patients whose age at onset of symptoms is less than 18 years, meet the above criteria for idiopathic inflammatory myopathy, and have heliotrope rash, Gottron papules or Gottron sign, are deemed to have juvenile dermatomyositis [125, 126].

11. MANAGEMENT

Treatment decisions are often based on expert opinion as very few randomized, placebo-controlled trials exist because of the rarity of the disease and lack of standardized tools to measure treatment outcomes [7]. For mild to moderate active muscle disease, early and aggressive treatment with high-dose oral prednisone (1 to 2 mg/kg/day [maximum 80 mg/day] in two divided doses) alone or ideally in combination with a steroid-sparing immunosuppressive agent (preferably, methotrexate 15 mg/m^2 [maximum 25 mg/dose] once a week either orally or subcutaneously) is the cornerstone of management [26, 91, 127, 128]. Pulse intravenous methylprednisolone (30 mg/kg/day [maximum 1g/day]) for 3 or more consecutive days is often preferred to oral prednisone in more severely affected patients, patients who respond poorly to oral prednisone, and patients with gastrointestinal vasculopathy [6, 18, 91]. Intravenous methylprednisolone can be stepped down to oral prednisone once the condition has stabilized. Some authors use intravenous methylprednisolone and oral prednisone concomitantly to increase the rate of response [41]. If there is a response to treatment, the dose of prednisone can be tapered slowly after 4 to 6 weeks of treatment [18, 41]. The total duration of corticosteroid treatment depends on the response of treatment and ranges from 4 to 24 months [18].

There are multiple systemic adverse events associated with the prolonged use of oral corticosteroids. These include hypertension, hyperglycemia, Cushing syndrome, hypothalamic-pituitary-adrenal suppression, growth retardation, cataracts, glaucoma, steroid-induced myopathy, and osteopenia/osteoporosis [118, 119, 129]. In this regard, children are more vulnerable to steroid adverse events than adults [11, 119]. Immunosuppressive agents (*e.g.*, methotrexate, cyclosporine, azathioprine, cyclophosphamide) have steroid-sparing and/or additive effects, and therefore, are often used in conjunction with corticosteroids to minimize the adverse effects of steroid therapy [43]. Of all the steroid-sparing agents, methotrexate, a folic acid analogue that inhibits nucleic acid synthesis, is preferred because of greater efficacy and fewer side effects [11, 31, 41, 112, 129]. Adverse events include nausea, vomiting, abdominal pain, headache, anemia, and less commonly, aphthous ulcers, temporary hair

loss, hepatic dysfunction, pulmonary dysfunction, and bone marrow suppression [31]. The adverse events are usually transient and disappear once methotrexate is discontinued [11]. Children on methotrexate treatment should be given folic acid 1 mg once a day or leucovorin (folinic acid) 5 mg once a week to limit toxicity from methotrexate treatment [41]. Cyclosporine (3 to 5 mg/kg once daily or divided into two daily doses) is usually reserved for refractory cases as its use is associated with more adverse events [11, 41, 130]. Adverse events include hypertrichosis, gingival hypertrophy, headache, nephrotoxicity, hepatotoxicity, bone marrow suppression, and increased susceptibility to infection [41]. Also, the risk of posterior reversible encephalopathy syndrome is increased in patients treated with cyclosporine and corticosteroid concomitantly [11]. Nevertheless, the use of cyclosporine remains an option in patients in which contraindications or intolerance to methotrexate exist [27]. Azathioprine may be used in lieu of methotrexate in the treatment of refractory juvenile dermatomyositis if methotrexate is not tolerated [11]. The recommended dose is 1 mg/kg/day for two weeks and 2 mg/kg/day subsequently [11]. Cyclophosphamide (500 mg/m^2 given intravenously every 4 weeks) is typically reserved for severe and life-threatening diseases, systemic involvement or cutaneous ulceration, in addition to high-dose corticosteroid therapy [7, 114, 131]. Generally, the medication is well tolerated. Adverse events include nausea, vomiting, abdominal pain, diarrhea, hyperpigmentation of the skin and nails, temporary alopecia, hemorrhagic cystitis, and sterility [11, 131].

Hydroxychloroquine (5 mg/kg/day [maximum 400 mg] given orally) may be a new therapeutic approach for the treatment of juvenile dermatomyositis with predominately cutaneous manifestations [27, 132]. The medication works by inhibiting the chemotaxis of eosinophils and impairing complement-dependent antigen-antibody reactions. The use of hydroxychloroquine for patients with skin predominant juvenile dermatomyositis has been recommended by the Childhood Arthritis and Rheumatology Research Alliance (CARRA) [132]. Adverse events associated with the use of hydroxychloroquine include hyperpigmentation of the skin and nails, pruritus, xerosis, urticarial and lichenoid skin rashes, hair discoloration, alopecia, exacerbation of psoriasis, Steven-Johnson syndrome, nausea, abdominal pain, diarrhea, corneal and posterior subcapsular lens opacity, retinopathy, prolongation of QT-interval, cardiomyopathy, hepatic dysfunction, and ochronosis [133].

Intravenous immunoglobulin can be used as an adjunctive second-line treatment option for refractory or recalcitrant cases [18]. The dose of intravenous immunoglobulin is 1 to 2 g/kg (maximum 70 g) administered as a single dose every 2 weeks for 3 to 5 times and then monthly for up to 2 years [11]. Alternatively, intravenous immunoglobulin can be given in monthly infusion starting from the first dose [11]. Intravenous immunoglobulin works by downregulating proinflammatory cytokines, suppressing inducer B and T cells, augmenting suppressor T cells, blocking Fc receptors on macrophages, and blocking complement cascade. Intravenous immunoglobulin is generally well tolerated. Adverse events include malaise, lethargy, flu-like symptoms, headache, nausea, vomiting, diarrhea, flushing, myalgia, back pain, chest tightness, dyspnea, tachycardia, and anaphylactic reactions (especially in IgA-deficient patients) [11, 31, 91]. As such, testing for immunoglobulin A deficiency should be performed prior to the administration of intravenous immunoglobulin [31].

For the treatment of calcinosis, some investigators advocate the use of bisphosphonates (alendronate/pamidronate), mycophenolate mofetil, intravenous immunoglobulin, infliximab, tofacitinib, abatacept, diltiazem, probenecid, intralesional corticosteroids, topical application of sodium thiosulfate, or surgical excision [72, 134-137]. Fractionated CO_2 laser may be used to assist the delivery of sodium thiosulfate [135].

A well-balanced diet as well as calcium and vitamin D supplements are crucial to prevent osteopenia/osteoporosis from steroid therapy [5, 3]. Topical corticosteroids and calcineurin inhibitors (*e.g.*, tacrolimus, pimecrolimus) can be used for the treatment of localised skin disease, particularly for symptomatic pruritus and erythema [91]. As the rash of juvenile dermatomyositis is generally photosensitive and aggravated by exposure to sunlight, avoidance of sun exposure especially during peak hours, regular use of high-factor sunscreens, and wearing of protective wide-brimmed hats and clothing when outdoors should be emphasized [5]. Physiotherapy and occupational therapy may help to improve muscle strength, support normal physical functioning, and prevent joint contractures [5, 21, 31]. Psychosocial assessment should be performed at disease onset and throughout the disease course and psychotherapy should be offered as needed [7]. Affected patients will benefit from a multidisciplinary approach that may involve the expertise of a dermatologist, rheumatologist, physical therapist, occupational therapist, neurologist, psychologist, nephrologist, cardiologist, gastroenterologist, endocrinologist, ophthalmologist, and surgeon [70].

12. PROGNOSIS

Since the introduction of corticosteroids as a therapeutic option and the advent of the early combination of immunosuppressive therapy, the mortality rate has dropped from over 30% to less than 2% [13, 16, 91, 138]. Approximately 20 to 40% of patients run a monocyclic course in which there is one disease episode within two years; those patients respond to standard treatment without relapse [42, 91, 139, 140]. Approximately 3% of patients run a polycyclic course with multiple relapses and remissions within two years [91]. The remaining 50 to 60% patients run a chronic persistent course for more than two years [43, 91, 139-141]. The skin disease tends to be persistent in a significant proportion of patients [142]. On the other hand, the muscle weakness tends to improve progressively to an acceptable functional recovery in most children with appropriate treatment, although they may retain some residual disability [17, 142, 143]. Disability is usually related to the severity of flexion contractures and the degree of calcinosis. Impairment of

muscle function may have a profound impact on the child's physical activities, leading to the need of wheelchair for mobility in approximately 5% of the affected children [17]. It has been shown that patients with juvenile dermatomyositis, both with active and inactive disease, have reduced cardiorespiratory fitness [143]. Major causes of mortality in patients with juvenile dermatomyositis include severe muscle weakness, superimposed infection, cardiac failure, perforation of the bowel, and respiratory failure [21].

CONCLUSION

Juvenile dermatomyositis, a chronic multisystemic autoimmune inflammatory disease involving children, is characterized by chronic inflammation of the skin and striated muscles as well as multi-systemic vasculitis. Diagnosis is usually straightforward in patients with typical clinical features but can be challenging otherwise. There is mounting evidence that early aggressive treatment improves outcomes. As such, physicians must be familiar with this condition so that an accurate diagnosis can be made and early aggressive treatment is initiated.

LIST OF ABBREVIATIONS

ACR	=	American College of Rheumatology
ALT	=	Alanine Aminotransferase
ANA	=	Antinuclear Antibody
Anti-Jo-1	=	Antibodies against Histidyl-tRNA Synthetase
Anti-MDA5	=	Antibodies against Melanoma Differentiation Associated Gene 5
Anti-Mi-2	=	Antibodies against Nuclear Helicase
Anti-NXP-2	=	Anti-nuclear Matrix Protein 2
Anti-SAE	=	Antibodies against Small Ubiquitin-like Modifier Activating Enzyme
Anti-SRP	=	Antibodies against Signal Recognition Particle
Anti-TIF1-gamma	=	Anti-transcription Intermediary Factor 1-gamma
Anti-U1-RNP	=	Antibodies against U1-ribonucleoprotein
AST	=	Aspartate Aminotransferase
C3	=	Complement 3
CARRA	=	Childhood Arthritis and Rheumatology Research Alliance
CBC	=	Complete Blood Cell Count
CHAQ	=	Childhood Health Assessment Questionnaire
CK	=	Creatine Kinase
CMAS	=	Childhood Myositis Assessment Scale
CRP	=	C-reactive Protein
DAS	=	Disease Activity Score
EMG	=	Electromyography
ESR	=	Erythrocyte Sedimentation Rate
EULAR	=	European League Against Rheumatism
HLA	=	Human Leukocyte Antigens
IL	=	Interleukins
JDMAI	=	Juvenile DermatoMyositis Activity Index
LDH	=	Lactate Dehydrogenase
MDAAT	=	Myositis Disease Activity Assessment Tool
MHC	=	Major Histocompatibility Class
MMT-8	=	Manual Muscle Testing of 8 Muscle groups
PRINTO	=	Paediatric Rheumatology International Trials Organization

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CONFLICT OF INTEREST

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