

## Inflammatory Myopathies in Children

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Juvenile idiopathic inflammatory myopathies (JIIM) are rare conditions that are probably autoimmune in nature. Childhood myositis is relatively more homogeneous than adult myositis; juvenile dermatomyositis (JDM) is by far the most common inflammatory myopathy, followed by far fewer cases of juvenile polymyositis, amyopathic dermatomyositis, overlap myositis, and inclusion body myositis. Childhood myositis differs also in the higher incidence of vasculopathy, often with intimal proliferation of small blood vessels, thrombosis, and sometimes infarction [1,2]. Although JDM is the most common presentation (with primarily skin and muscle manifestations), the underlying systemic vasculopathy can involve many systems. Treatment is directed toward reducing inflammation through immunosuppression. The disorders have a good outcome with favorable prospects for normal school and work performance, but many of the affected children will have a chronic disease and will require long-term therapy.

This article describes a recent patient who presented with typical JDM and uses her case to discuss aspects of the childhood inflammatory myopathies.

### The case

Kathryn is a 13-year-old white girl (Fig. 1) who met the diagnostic criteria of Bohan and Peter [1] at presentation. She initially was referred to the authors'

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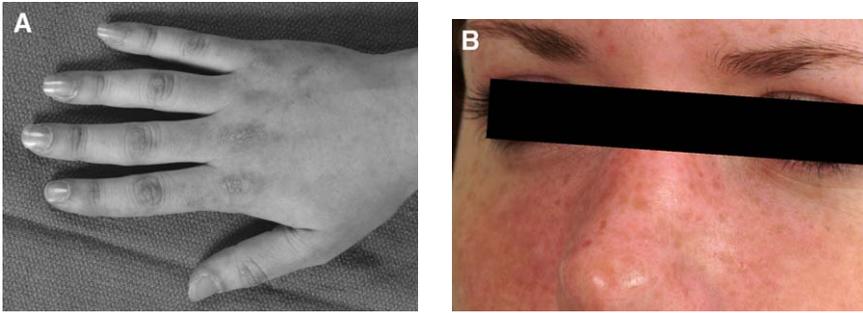


Fig. 1. (A) Patient's hand at the time of diagnosis showing a papulosquamous eruption on the extensor surface of the metacarpophalangeal and proximal interphalangeal joints (Gottron's papules). (B). Patient at diagnosis showing a malar (crossing the nasal bridge) and forehead rash as well as a heliotrope discoloration of the upper eyelids with mild edema.

by a dermatologist for typical Gottron's papules on her knuckles that developed within the 2 months before presentation. During 1 month she had developed progressive proximal muscle weakness associated with intermittent knee pain. On initial assessment, she had low-grade fever with malar rash and a heliotrope rash over the upper eyelids. She had evidence of Gottron's papules over her knuckles and elbows. Capillaroscopy (microscopic examination) of the nail beds showed capillary changes with decreased capillary density, dilatation, tortuosity, and dropout. She had symmetrical proximal muscle weakness, stress pain in the right knee, and an effusion in the left knee associated with pain and limited range of motion. Her laboratory results were in keeping with JDM. She had a significant increase of all the muscle enzymes and high-titer anti-nuclear antibodies (1/1280) with a speckled pattern; other measured autoantibodies were all negative. An MRI of the proximal muscles (upper and lower limb girdles) confirmed diffuse acute myositis with some atrophy of the paraspinal and gluteal muscles (Fig. 2). An electromyogram (EMG) was consistent with a myopathic

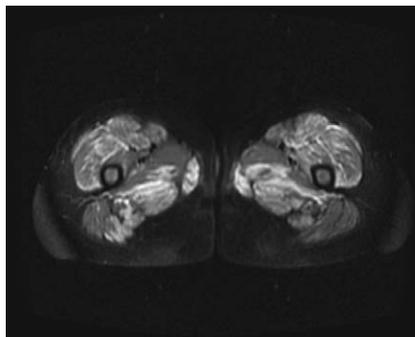


Fig. 2. Fat-suppressed T2 MRI of patient at diagnosis. The bright areas reflect edema and inflammation in the quadriceps and hamstring muscles bilaterally.

process. Because her presentation and laboratory findings were typical, she did not undergo muscle biopsy. The rest of the clinical and laboratory examination was normal, ruling out any other organ involvement. She initially was treated with high-dose oral corticosteroids (approximately 2 mg/kg divided into three doses) and experienced some improvement, but significant proximal muscle weakness persisted. Because of her incomplete response, she received three pulses of high-dose intravenous methylprednisolone (30 mg/kg/dose) 6 weeks after presentation with an excellent clinical response. She had also started treatment with methotrexate (MTX) at presentation. Now, a few months later, her corticosteroids are being tapered; she will probably discontinue prednisone at about 10 months after presentation but will continue taking MTX. She is doing well clinically. Her strength is normal, the rash has cleared, and her muscle enzyme tests are all normal, but she continues to have a mildly elevated erythrocyte sedimentation rate.

## Epidemiology

Kathryn's presentation suggests several questions of an epidemiologic nature. How common is a case like this? Does ethnicity play a role in the frequency of JIIM? Is 13 years a typical age of presentation? Is it unusual to see JDM presenting in a girl?

It would seem from the literature that JIIM are quite rare. Several recent studies have demonstrated an incidence of about two to three cases per million children per year. For example, a survey study in Great Britain suggested that the incidence of JDM is about 1.9 per million children below 16 years of age [3]. More recently, data from a National Institutes of Health-sponsored registry have suggested that the incidence rate of JDM in the United States, between 1995 and 1998, ranged in different states from 2.5 to 4.1 per million children, with an average annual incidence rate of 3.2 per million children below the age of 17 years [4]. Childhood myositis is much more rare than the inflammatory myopathies in adults; in one series of 124 patients with myositis, only 21% of the patients were under 15 years of age at diagnosis [5]. At the Hospital for Sick Children Myositis Clinic in Toronto, a city with a population in the metropolitan area of about 4.5 million persons, the authors have followed 137 children with JIIM (121 with JDM, 5 with amyopathic JDM, 5 with juvenile polymyositis, and 6 with overlap connective tissue diseases) in the last 14 years. Worldwide, it seems that JIIM are quite rare.

Unlike some other autoimmune diseases, (eg, systemic lupus erythematosus) there does not seem to be an over-representation of black or Asian patients. In the American registry study, there was a predominance of white non-Hispanic children (65.1%), followed by Hispanic (14.2%) and African-American non-Hispanic (11.4%) children [4]. At the Hospital for Sick Children, about 81% of the patients are white, 6% are East Indian, 6% are Asian, 5% are African-

Canadian, and 2% are Native Canadian. Given the small numbers of patients, these figures probably reflect the ethnic distribution of the population served.

JiIM often develops during the school-age years. For example, in the British nation-wide study, the median age at onset was 6.8 years [3]. Likewise, at the Hospital for Sick Children, the median age at diagnosis is 7 years. The youngest patient was 1.2 years of age at diagnosis (patients younger than this would probably be given the diagnosis of infantile myositis, which is not included in the authors' series). Two thirds of the authors' patients were diagnosed between the ages of 4 and 11.5 years.

Girls are usually affected more often than boys. The sex ratio has varied greatly in the reported studies, however, ranging from 1:1 in Singapore for children under the age of 5 years [6] to 5:1 (girls:boys) in the British series [3]. At the Hospital for Sick Children, the sex ratio has consistently been about 2:1 (girls:boys) over the years.

This patient, then, although a bit older than most newly diagnosed children, is not otherwise unusual, considering the rarity of the disorder overall.

## **Etiology and pathogenesis**

Why did Kathryn develop JDM? She did not have a family history, nor did she have a personal history of a clear exposure to an infectious or environmental agent.

The etiology and pathogenesis of JiIM are unknown. Many potential pathogenic mechanisms have been suggested, including a genetic predisposition, the role of triggering factors such as infectious agents, and the role of complement and soluble adhesion molecules [7,8]. Like other presumably autoimmune diseases, the JiIM probably result from interactions with environmental agents in a genetically predisposed host.

### *Genetic predisposition*

Three lines of evidence suggest that children who develop JiIM have a genetic predisposition. First, there is a relatively strong association with certain major histocompatibility complex (MHC) alleles and the development of myositis. Second, maternal microchimerism has been discovered at a higher frequency in children with myositis. Third, children who inherit high-producing tumor necrosis factor (TNF) genes have a more severe and longer-lasting form of juvenile myositis than those who do not have these genes.

The MHC antigens determine, among other things, the antigens to which an individual's immune system can react. It is possible that only certain people inherit MHC molecules that can present the autoantigens important in the development of JiIM. For example, the MHC antigen HLA-DQA1\*0501 has

been proved to be important in JIIM susceptibility in several ethnic groups. Reed and Stirling [9] studied 70 patients with JDM and found that 87% of African-American patients, 92% of Hispanic patients, and 86% of white patients had this allele (versus 33%, 28%, and 46% of controls, respectively). Other MHC class I and II alleles have been shown to be involved in disease susceptibility [10]. The HLA-DMA\*0103 and HLA-DMB\*0102 alleles are significantly more frequent in patients with JDM [11].

Maternal microchimerism (ie, the persistence of maternal blood cells transferred by the placenta during fetal development) has been identified in CD4 or CD8 peripheral blood cells and in the inflammatory lesions of the skin and the muscle of children with JIIM. Microchimerism, which seems to be involved in the pathogenesis of systemic sclerosis, might be responsible for inducing a graft-versus-host response manifesting as autoimmune disease [12–15]. Mothers' HLA genotypes may facilitate the transfer and the persistence of chimeric cells in the circulation of their children with JDM [15]. Contradictory data have been reported about the association of HLA-DQA1\*0501 and microchimerism, however [14–16]. Artlett et al [16] did not find any association between the DQA1\*0501 allele (in the donor or in the recipient) and the existence of microchimerism in children with JIIM, whereas Reed et al [15] recently demonstrated that the presence of microchimerism in the JDM patients is associated with the DQA1\*0501 allele in the mother. Either way, chimeric cells may play an important role in JIIM pathogenesis. For example, maternal-derived chimeric T cells have been shown to develop a memory response to the children's lymphocytes.

TNF- $\alpha$  is an immunomodulator and proinflammatory cytokine that has been implicated in the pathogenesis of autoimmune diseases. TNF- $\alpha$  gene polymorphisms have been reported to be associated with several rheumatic diseases [17]. The first polymorphism described raised the hypothesis that this polymorphism may contribute to autoimmunity [18]. It has been shown more recently that this polymorphism, identified by a G-to-A substitution at the NCOI restriction site, is a strong transcriptional activator that has direct effects on TNF- $\alpha$  gene regulation and is associated with a high-producing TNF- $\alpha$  phenotype [19]. The association between increased production of TNF- $\alpha$ , long disease duration, and pathologic calcification has been investigated in JIIM. A long disease course (> 36 months) and the development of calcification were found to be associated with the TNF- $\alpha$  allele substitution (along with an increased TNF- $\alpha$  production, which may lead to the perpetuation of the inflammatory response) [20]. TNF- $\alpha$  expression in the muscle fibers of affected patients has been recently investigated. An untreated JDM patient who had the TNF- $\alpha$ -308A allele had an increased number of TNF- $\alpha$  stained muscle fibers. It has been suggested that increased local TNF- $\alpha$  production may prolong muscle fiber damage [21]. It has also been demonstrated that the TNF- $\alpha$ -308A allele is associated with increased circulating concentrations of thrombospondin-1, an anti-angiogenic factor that may play a role in the increased vascular occlusion seen in children with JDM who have the TNF- $\alpha$ -308A allele [22].

Taken together, these findings suggest that some children inherit a number of genes that, perhaps in combination, predispose them to the development of JIIM.

### *Role of infectious agents and environmental factors*

A number of infectious agents and other environmental triggers have been suspected in the pathogenesis of JIIM. Rider et al [23] have summarized some of these agents (Table 1). At present, there is not strong epidemiologic or clinical evidence to support any environmental agent in the pathogenesis of JIIM.

Massa et al [24] have suggested a mechanism of molecular mimicry that might act as a trigger of an abnormal immune response leading to JDM: an abnormal response to a microbial antigen that is homologous to a self-antigen may induce the disease. It has been shown that self-epitopes in the human skeletal myosin heavy chain are homologous to specific amino acid sequences in the M5 protein of *Streptococcus pyogenes*. Recognition of these self-epitopes in skeletal muscle triggers activation of disease-specific cytotoxic T cells; these cells are responsible for a cytotoxic response to the M5–Myo peptide pair and may be associated with active disease. Other common pathogens, such as *Borrelia burgdorferi*, *Mycoplasma hominis*, *Haemophilus influenzae*, *Helicobacter pylori*, *Escherichia coli*, and *Bacillus subtilis*, share sequence homologies with the Myo peptide of human skeletal myosin [24].

Finally, gene-expression profiles have been studied in patients with untreated JDM who were positive for the DQA1\*0501 allele. Interferon-inducible genes were dysregulated in the muscle biopsies of these patients compared with controls. This pattern of gene expression is consistent with an interferon (IFN)- $\alpha\beta$  transcription cascade supporting the hypothesis of a host defense mechanism against infection. Both IFN- $\alpha\beta$  and IFN- $\gamma$  cascades may lead to muscle ischemia and increased production of TNF $\alpha$  and nitric oxide and may potentially inhibit regeneration of necrotic muscle fibers [25].

Table 1  
Triggering factors associated with juvenile idiopathic inflammatory myopathies

Bacteria	A hemolytic streptococcus, <i>Borellia</i> spp
Virus	Hepatitis B, RNA picornaviruses, Cocksackie virus B, Echovirus, Influenza, Parainfluenza, Parvovirus B19, HTLV-1
Parasites	<i>Toxoplasma gondii</i> , trichinosis, filiarisis
Vaccines	Hepatitis B, MMR, typhoid, cholera
Medications	D-penicillamine, carnitine, GH
Bone marrow transplantation	Graft-versus-host myositis
Ultraviolet light	Unusual sun exposure

*Abbreviations:* GH, growth hormone; HTLV-1, human t cell lymphotropic virus type 1; MMR, measles, mumps, rubella.

*From* Rider LG, Miller FW. Classification and treatment of the juvenile idiopathic inflammatory myopathies. *Rheum Dis Clin North Am* 1997;23(3):619–55; with permission.

Although unproven, it certainly seems plausible that infectious or other environmental agents can trigger JIIM. Studies suggest that if genetically susceptible patients are exposed to one or several of these agents, they may develop the disease.

Some of the immune mechanisms that seem to be responsible for the inflammatory change seen in JIIM are now known. Complement-mediated damage of vessels seems to occur uniformly in JDM patients. Adhesion molecules are overexpressed and may lead to recruitment of inflammatory cells around vessels and in muscle. MHC class I molecules are expressed early in JIIM muscle and may lead to further development of an inflammatory reaction locally.

### *Role of complement*

Complement-induced injury seems to be a major mechanism in JDM. Activated complement, which has been shown to occur in JIIM, might induce further cytokine release and vessel injury. The activation of the complement cascade leads to cellular damage mediated by the membrane attack complex (MAC) and is probably responsible for capillary damage in JDM [26]. The factors triggering vascular damage, antibody deposition, and complement activation are not known. CD59 is present in the sarcolemma of human skeletal muscle fibers. CD59 regulates MAC by preventing its full assembly and its deposition in vessels. In JDM, the expression of CD59 is decreased in the muscle fibers and vessels, potentially leading to increased local activation, vessel damage, and muscle ischemia; deposition of MAC is increased in the vessels but not in non-necrotic muscle fibers [27].

### *Role of soluble adhesion molecules*

Adhesion molecules such as intracellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM-1) belong to the immunoglobulin gene superfamily. These molecules may encourage local recruitment of inflammatory cells. ICAM-1 expression on endothelial cells seems to be increased consistently in capillaries and perimysial large vessels; it is increased occasionally in the endomysial large vessels. VCAM-1 expression is increased inconsistently, mostly in the perimysial large vessels, and is usually surrounded by an inflammatory infiltrate [28]. This phenomenon might be linked to complement activation, because the binding of C5a to endothelial cells may increase the expression of adhesion molecules.

### *Role of major histocompatibility complex class I expression*

Constitutive MHC class I expression in normal muscle is low. A recent study has shown that MHC class I heavy-chain and  $\alpha 2$  microglobulin are both overexpressed in the muscle fibers of children with JDM. (This finding is also seen in adults with myositis.) MHC class I expression seems to be an early

phenomenon, occurring in the muscle before significant inflammatory changes are seen [29]. Although the pathogenic role of MHC class I in JIIM patients is not yet clear, some believe that expression of these molecules is an important early step in the initiation of a local inflammatory response.

### Classification and diagnostic criteria

When Kathryn was referred to the Hospital for Sick Children, a diagnosis had not yet been made. It is appropriate to discuss how best to make a diagnosis of the JIIM and how best to classify these disorders.

Most centers still use the diagnostic criteria and classification system proposed in 1975 [1,30]. There have been and continue to be attempts to update these criteria to take into account a broader understanding of the clinical and immunologic heterogeneity of the JIIMs and to incorporate newer diagnostic technologies.

Bohan and Peter [1,30] proposed five major diagnostic criteria for polymyositis and dermatomyositis in 1975. These five criteria, summarized in Table 2, are still widely used as standard criteria.

Table 2  
Diagnostic criteria for the inflammatory myopathies in adults and children

Criteria	Description
Muscle involvement	Symmetrical and progressive proximal muscle weakness ( $\pm$ dysphagia and respiratory involvement)
Muscle biopsy	Necrosis of type I and II fibers Phagocytosis Regeneration with basophilia Large vesicular sarcolemmal nuclei Prominent nucleoli Atrophy in a perifascicular distribution Variation in fiber size
Elevation of muscle enzymes	Inflammatory exudates, often perivascular Particularly creatine phosphokinase Often aldolase AST, lactate dehydrogenase
Electromyogram	Short, small, polyphasic motor units, fibrillations, positive sharp waves Insertional irritability
Dermatologic features	Bizarre, high-frequency repetitive discharges Lilac discoloration of the eyelids (heliotrope) with periorbital edema Scaly and erythematous dermatitis over the dorsum of the hands (Gottron's sign) Involvement of the knees, elbows and medial malleoli, face, neck and upper torso

*Adapted from* Bohan A, Peter JB. Polymyositis and dermatomyositis [part 1 of 2]. *N Engl J Med* 1975;292(7):34–7; with permission.

According to the 1975 criteria, a diagnosis is considered definite if a patient presents with three or four criteria (plus the rash) for dermatomyositis and four criteria for polymyositis. The diagnosis is considered probable if the patient presents two criteria plus the rash for dermatomyositis and three for polymyositis. The diagnosis is considered possible if fewer criteria are present.

In this schema, IIM are classified into five groups: group I, primary idiopathic polymyositis; group II, primary idiopathic dermatomyositis; group III, dermatomyositis (or polymyositis) associated with neoplasia; group IV, childhood dermatomyositis (or polymyositis) associated with vasculitis (vasculopathy); and group V, polymyositis or dermatomyositis associated with collagen-vascular disease (overlap polymyositis) [1].

More recently, Rider et al [23] have proposed a clinico-pathologic classification (Table 3) along with a serologic classification of JIIM. The serologic classification is used in adult patients, in whom myositis-specific antibodies (MSA) are more common and in whom these MSA may define more homogeneous subsets of patients. Some evidence suggests that, when present, MSA

Table 3

Clinicopathologic classification suggested for juvenile idiopathic inflammatory myopathies

Disorder	Description
Juvenile dermatomyositis	Most common juvenile idiopathic inflammatory myopathy Pathogenesis humorally mediated with CD4+ T cells and B cells in a perivascular distribution Characterized by small vessel thrombosis
Juvenile polymyositis	Pathogenesis cellularly mediated with CD8+ T-cell endomysial inflammation
Overlap myositis	Usually mild myositis with polycyclic course
Orbital or ocular myositis	Reported rarely in children Frequent association with other autoimmune disease
Cancer-associated myositis	Reported rarely in children
Focal and nodular myositis	Focal pain and swelling Reported rarely in children
Proliferative myositis	Pseudosarcomatous proliferation of giant cells and fibroblasts with associated inflammation and necrosis Rare in childhood
Inclusion-body myositis	Proximal and distal muscle weakness Low creatinine phosphokinase Rimmed vacuoles on trichrome muscle biopsy Reported rarely in children
Dermatomyositis sine myositis	Myositis may be sub-clinical
Eosinophilic myositis	Reported rarely in children
Granulomatous myositis	Idiopathic or in association with sarcoidosis Rare in childhood

*Adapted from* Rider LG, Miller FW. Classification and treatment of the juvenile idiopathic inflammatory myopathies. *Rheum Dis Clin North Am* 1997;23(3):619–55; with permission.

may define clinical subsets in children as well. Similarly, MSA that are associated with other connective tissue diseases may define more homogeneous groups of patients [23]. The serologic classification for children is somewhat controversial, however, because no specific autoantibodies are found in most patients with JIIM [31].

MRI has been recently proposed to detect skin, fascia, and subcutaneous abnormalities along with subclinical muscle involvement, providing potential help in classifying the difficult cases. MRI may become one of the diagnostic criteria, possibly replacing more invasive and painful investigations (such as EMG and muscle biopsy) in otherwise straightforward cases. Its cost and restricted availability makes its use in routine practice difficult in some parts of the world [32,33].

### Diagnostic work-up

Kathryn had a number of tests at the time of diagnosis that allowed the authors to reach a diagnosis within the context of the Bohan and Peter criteria. What other tests should be done at diagnosis?

The initial assessment includes the recognition of a therapeutic emergency, such as respiratory distress or swallowing difficulties related to severe muscle weakness. Once these issues have been ruled out, the goal of the work-up is to confirm the first clinical impression and to classify the JIIM to start the treatment as soon as possible. (Because the management of most JIIM is the same, classification in some cases is a somewhat academic exercise.) The usual diagnostic work-up in the Myositis Clinic of the Hospital for Sick Children includes

1. Clinical examination (with recognition of the diagnostic criteria of Bohan and Peter along with other organ involvement)
2. Exclusion of mimics and other conditions in the differential diagnosis (Table 4)
3. Laboratory investigations including
  - a. Serum levels of muscle enzymes
  - b. Markers of inflammation (eg, erythrocyte sedimentation rate, C-reactive protein)
  - c. Autoantibodies (ie, anti-nuclear antibodies as well as antibodies specific for other diseases, such as anti-ds-DNA, anti-Sm, anti-RNP)
  - d. Infectious studies and serology as indicated
  - e. MRI of the proximal muscles (fat-suppressed T2 or short tau inversion recovery sequences)
  - f. EMG
  - g. Muscle biopsy (considered when the results of the preliminary work-up are not conclusive)
4. Chest radiograph

5. Pulmonary function tests with measurement of maximal pressures and diffusing capacity
6. ECG
7. Nailfold capillaroscopy (If specialized microscopy is not available, the nailfold capillaries can be visualized by placing water-soluble gel on the skin just proximal to the nail and using a magnified light source such as an otoscope or ophthalmoscope at a setting of +20 or +40.) (Fig. 3)
8. Consultation by the neuromuscular service and rheumatology

Table 4

Differential diagnoses for juvenile idiopathic inflammatory myopathy

Category	Possible entities
Muscular dystrophies (X-linked, autosomal dominant or recessive)	Duchenne's disease Becker's
Congenital myopathies	Congenital muscular dystrophy
Myotonic disorders	Congenital myotonic dystrophy
Metabolic disorders	Glycogen storage disease Certain enzyme deficiencies Familial periodic paralysis Endocrinopathies (Cushing's, hypothyroidism) Chronic dialysis
Infectious/postinfectious myopathies	Viral (Influenza B, Coxsackie B, Echovirus, and Poliomyelitis) Toxoplasmosis Trichinosis, cysticercosis Septic (staphylococcus and other pyogenic myositis) Tetanus
Other connective tissue diseases	Scleroderma Mixed connective tissue disease Systemic lupus erythematosus Systemic arthritis
Genetic disorders	Osteogenesis imperfecta Ehlers–Danlos syndrome Mucopolysaccharidoses
Trauma/toxic	Physical Toxic: drugs (glucocorticoids, hydroxychloroquine, diuretics, alcohol, D-penicillamine, cimetidine, vincristine)
Spinal, muscular, and anterior horn-cell dysfunction	Infantile and juvenile muscle atrophy Arthrogryposis multiplex congenital Amyotrophic lateral sclerosis
Peripheral nerve dysfunction	Charcot–Marie–Tooth disease Neurofibromatosis Guillain–Barré syndrome
Disorders of neuromuscular transmission	Congenital myasthenia gravis Botulism

*Adapted from* Cassidy JT, Petty RE. Juvenile dermatomyositis. In: Textbook of pediatric rheumatology. 4th edition. 2001. p. 465–504, with permission; Pachman LM. Juvenile dermatomyositis. Pathophysiology and disease expression. *Pediatr Clin North Am* 1995;42(5):1071–98.

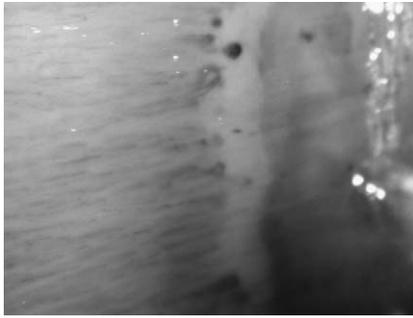


Fig. 3. Photomicrograph (magnification  $\times 20$ ) of the distal nailfold vessels of a patient with JDM, showing an avascular strip just proximal to the nail with more proximal dilated capillary vessels and some dot hemorrhage.

An upper gastrointestinal series and swallowing study may be of interest if there is any clinical suspicion of gastrointestinal involvement.

### **Clinical features**

Kathryn presented with mild systemic symptoms and more marked musculoskeletal and dermatologic complaints. What other clinical signs and symptoms might have been seen?

#### *Constitutional signs and symptoms*

In some series, fever at onset has been described as a frequent occurrence. Only about 20% of the authors' patients have presented this way, but fatigue (probably related to muscle weakness), malaise, anorexia, and weight loss have been frequent early complaints. In young children, irritability and developmental regression have been described [8].

#### *Musculo-skeletal manifestations*

JDM is characterized by weakness; the weakness, which probably affects all muscle groups, is most obvious in the limb-girdle musculature, the anterior neck flexors, and the trunk muscles. The muscle groups that seem to be the most affected are the shoulders, the hips, the neck flexors, and the abdominal musculature. The affected muscles may be occasionally tender, edematous, or indurated. Gower's and Trendelenberg's signs are typical early findings on examination. Distal muscle weakness is more obvious in the children who overall are more severely affected. Almost one fourth of the authors' patients present with involvement of the pharyngeal, hypopharyngeal, and palatal muscles. This

involvement manifests clinically by difficulty in swallowing, dysphonia, nasal speech, and regurgitation of liquids through the nose. The risk of aspiration in this state seems to be high, and great care must be taken with feeding. Parenteral feeding is sometimes needed until pharyngeal weakness has resolved.

Arthralgia and mild, transient, nondeforming, nonerosive arthritis has been described [34–36]. The arthritis usually occurs early in the course of the disease (within the first 6 months) and frequently involves knees, wrists, elbows, and fingers. The initial arthritis can be pauciarticular (67%) or polyarticular (33%). The arthritis generally shows a good response to JIIM therapy, but recurrences are seen during corticosteroid tapers [37]. The evolution into chronic polyarthritis occurs less often [38]. Tenosynovitis or flexor nodules may be present. Flexion contractures are common but in many cases seem to reflect muscle tightening rather than joint capsule disease. In the presence of significant arthritis, an overlap syndrome (with features of lupus, juvenile rheumatoid arthritis, or scleroderma) should be considered.

### *Cutaneous manifestations*

The rash seen in JDM is the hallmark of the disease and is present in all cases [8,34,39]. The most typical features (heliotrope eyelid rash and Gottron's papules) are pathognomonic and are seen in about 80% of patients. The rash may occur before or after the occurrence of clinical weakness [40].

Gottron's papules are sometimes also called collodion patches [41]. They are flat-topped, violaceous or red papules, which can be scaly. A similar non-palpable (macular) rash is called Gottron's sign. This papulosquamous rash is located over the extensor aspect of the knuckles (metacarpophalangeal, proximal, and distal interphalangeal joints), elbows, knees, and the medial malleoli. Over time, the lesions may develop an atrophic white center with telangiectasia. The rash usually spares the interphalangeal spaces [40]. Early in the disease, Gottron's papules over the knuckles may be confused with flat warts [39].

The heliotrope rash over the upper eyelids (with or without edema of the eyelids or the face) is highly characteristic of JDM [41]. It may be a component of a more diffuse malar or facial rash that does not seem to spare the nasolabial folds (which may help differentiate the JDM rash from lupus).

Nailfold capillary and cuticular changes are characteristic of JDM and are part of the systemic vasculopathy. Capillary changes can also lead to gingival telangiectasia [42]. Endothelial cell proliferation and capillary basement membrane thickening leads to vascular occlusion and decreased tissue perfusion [39]. Direct visualization of the capillary beds may reveal areas of new vessel growth in response to these processes. The nailfold capillary changes seen in JIIM include capillary dropout (ischemia leading to capillary loss) leading to end row capillary loss, dilated capillary loops (hemodynamic changes leading to change in vascular morphology), and branching arboreal capillary loops (neovascularization leading to bushy loops). These changes are positively correlated with disease activity [43] and duration of untreated disease [44]. In

one study, the loss of end row nailfold capillary loops was related to skin disease activity, suggesting that skin involvement is mainly a reflection of the vasculopathy [44]. The vasculopathic lesions are more common in JDM than in adult dermatomyositis, as are cutaneous calcinosis and lipodystrophy [41]. Almost 100% of the children with JDM have decreased capillary density at the nailfold. Cuticular hypertrophy may also be present in JDM [39].

A photosensitive macular erythematous or violaceous rash may involve the upper chest (V-sign), neck, shoulders (shawl-sign), extremities, hands, scalp, and face. It may evolve into poikiloderma (hyper- or hypo-pigmentation with atrophy and fine telangiectasia) [39].

Other skin rashes may be seen. Mechanic's hands (scaly hand dermatitis) may be present even though it seems to be more common in adult myositis [41]. Pruritus and psoriasiform scalp dermatitis may be seen at presentation. Periungual infarcts and cutaneous and mucosal ulcers may be present at or a few months after the initial presentation [40]. Ulcers at the corners of the eyes, in the axillae, over the elbows, or at pressure points may be signs of systemic vasculitis. Children who have a generalized rash and cutaneous ulceration at onset may have the worst prognosis [45], because the ulceration presumably reflects a more extensive vasculopathy. Edema and induration of the skin and of the subcutaneous tissue may be seen, particularly in the periorbital area, the face, and the distal extremities. (When edema is present at the distal extremities, there may be the appearance of "Popeye" arms.)

### *Calcinosis*

Dystrophic calcinosis (Fig. 4) is a characteristic complication of JDM reported in 30% to 70% of the patients in various series [35]. Cutaneous calcifications are often located on the elbows, knees, and other acral parts but can be located anywhere. These lesions can lead to local pain, joint contracture, and overlying skin ulcers.



Fig. 4. Superficial calcinosis with some skin ulceration around the right knee of a patient with JDM.

The mechanism of calcinosis is thought to be dystrophic. Damaged muscles release mitochondrial calcium into matrix vesicles that promote mineralization. Histologic study has shown that calcinosis is related to hydroxyapatite accumulation [46].

Dystrophic calcification can also be located at sites of trauma and may result in more severe disease or disease of longer duration. Calcinotic lesions are rarely present at diagnosis but are seen later during the course of the disease [34,39]. Calcinosis can occur as superficial lumps, deep tumorous deposits around joints, or plates along fascial planes, or the lesions may have a widespread exoskeleton distribution. Delayed treatment and severe disease are risk factors for developing calcinosis [34,47]. Aggressive treatment of JDM is hoped to result in a decreased frequency of calcinosis [48–50].

### *Lipodystrophy*

Lipodystrophy and associated metabolic abnormalities are well-known complications of JDM. It is less clear that this problem arises in the other JIM. Rarely seen at presentation, these changes develop later in the course of the disease in 14% to 25% of patients [39,51]. Lipodystrophy is characterized by a progressive, slow, and symmetrical loss of subcutaneous fatty tissue that mainly involves the upper body. There may be a female preponderance. Lipodystrophy belongs to a wider condition including generalized or localized partial loss of subcutaneous fat, hirsutism, and acanthosis nigricans associated with hepatomegaly, insulin-resistant diabetes mellitus, and hyperlipidemia, especially hypertriglyceridemia [52]. It has been reported recently that 20% of 20 patients in Vancouver had lipodystrophy and either diabetes mellitus or impaired glucose tolerance, whereas 40% had abnormal glucose or lipid studies without lipodystrophy [51]. The physiopathology of this condition is currently unknown, although it is likely that hyperinsulinemia results in many of the clinical features. Hyperinsulinemia in JDM is probably multifactorial, but muscle inflammation with resulting metabolic derangements and prolonged exposure to corticosteroids are probably involved. (Counter-regulatory hormones may play a role in this setting.)

### *Gastrointestinal involvement*

Esophageal dysmotility and malabsorption with decreased absorption of nutrients, and perhaps of oral medications, have been described. Case reports of pancreatitis, cholestasis, and hepatomegaly have been reported in JDM. Clinically severe vasculopathy of the gastrointestinal tract leading to functional problems, pain, altered stool patterns, and gastrointestinal bleeding or even perforation can be one of the most serious manifestations of JIM, especially JDM.

### *Vasculitis*

The presence of visceral vasculopathy, although rare, is associated with poor prognosis. It is unclear whether true vasculitis (ie, necrotizing arteritis, or leukocytoclastic small vessel vasculitis) occurs in JIIM. In any case, the vasculopathy that is seen can lead to diffuse ischemia of the gastrointestinal mucosa (responsible for ulceration, perforation, or hemorrhage) or to acute mesenteric infarction. Rarely, the vasculopathy can also affect the gallbladder, the urinary bladder, uterus, vagina or testes, and central and peripheral sensorimotor systems. Retinitis with cotton-wool exudates is a rare ophthalmologic manifestation of vasculopathy.

### *Pulmonary involvement*

Lung manifestations are seen much less often in JIIM than in adult myositis. The authors have had very few cases of parenchymal disease at the Hospital for Sick Children (2 of 137 patients). Respiratory weakness and resultant symptoms are more common: one third of their patients had some degree of pulmonary signs or symptoms during the course of the disease [39]. In one recently reported series, the pattern of pulmonary involvement was an asymptomatic restrictive pattern with impairment of diffusion seen in 5 of 12 patients at presentation [53]. Reduction in ventilatory capacity has been found in up to 78% of asymptomatic JDM patients, probably in keeping with respiratory muscle weakness [54]. Decreased diffusion capacity as an early sign of interstitial lung disease has been reported in children who develop anti-Jo-1 antibodies (a type of MSA) [55]. Serious pulmonary disease can occur but fortunately is seldom seen.

Pulmonary disease may occur by two other mechanisms. Pharyngeal weakness may allow pathologic aspiration of food or secretions that can lead to atelectasis or pneumonia. In addition, children with JIIM are treated with immunosuppressive medications; in the setting of pulmonary disease, one must always consider the possibility of opportunistic lung infection. Although rare (the authors have not had a case of opportunistic pneumonia in the Myositis Clinic at the Hospital for Sick Children), fatal opportunistic infections have been reported in children with other autoimmune diseases [56].

### *Neurologic involvement*

Peripheral and central neurologic manifestations have been described in JIIM but are rare. When seen, central nervous system (CNS) disease has been in the setting of severe and refractory disease [57–59]. It is unclear whether CNS involvement is caused by vasculopathy or by specific vasculitis, because the series published so far have failed to demonstrate the presence of true vasculitis

on brain autopsy. The symptoms that have been reported have mainly been generalized tonic-clonic seizures with or without subsequent abnormal neurologic signs such as ptosis, hypertonia, flaccid hemiplegia, motor aphasia, and bulbar paresis or coma [57,58]. Other nonspecific symptoms, such as emotional lability and depression, have been reported; in the setting of a chronic disease, it may be difficult to relate these findings specifically to JIIM. Imaging findings in reported patients have ranged from normal to lacunar changes or multiple ischemic infarctions with severe emboli in the cortex on MRI. Several mechanisms have been evoked to explain this CNS involvement, including vasculopathy, CNS vasculitis, hypoxic-ischemic encephalopathy (hypoperfusion), hypertensive encephalopathy, or drug-induced toxicity [58].

#### *Cardiac involvement*

Specific cardiac involvement has not been well described in JIIM and is probably rare. In adult series, which have included some JIIM, nonspecific murmurs and ECG abnormalities as well as pericarditis have been reported and seem to be the most common cardiac findings [60]. There have been reports of ECG myocardial infarction, congestive heart failure, and more widespread cardiac vasculopathy in adults and children with JIIM [61–63].

#### *Ophthalmologic involvement*

Eye disease is unusual. Isolated case reports of retinopathy and bilateral membranous conjunctivitis have been published. Transient retinal exudates and cotton-wool spots may occur, leading potentially to optic atrophy and visual loss. Side effects of corticosteroids use, such as cataracts and glaucoma, may be seen [39]. The authors no longer recommend ophthalmologist follow-up for their patients; retinal disease is exceptional, and side effects of treatment that affect the eye can easily be detected by non-ophthalmologists (Akikusa, submitted for publication, 2004).

#### *Malignancy and juvenile idiopathic inflammatory myopathies*

Unlike adult DM, JDM is rarely associated with malignancy; there have been only a few case reports. The authors do not search for occult malignancy in their patients.

#### *Juvenile polymyositis*

Juvenile polymyositis (JPM) is a rare condition. Although the term is used to describe idiopathic myositis without any skin rash, it is possible that some children should really be labeled as having dermatitic dermatomyositis. That is,

although there is no skin rash, these patients have a muscle pathology that is identical to JDM (eg, vasculopathy, perifascicular atrophy) rather than to adult polymyositis. JDM and JPM patients are managed similarly and for the most part seem to respond similarly.

### *Amyopathic juvenile dermatomyositis*

The term amyopathic JDM refers to a disorder in which the characteristic skin rash of JDM is seen without apparent muscle inflammation. It is still not clear whether amyopathic JDM is a separate entity or is the extreme end of the spectrum of JDM with minimal muscle involvement. Diagnostic criteria for amyopathic DM have been proposed in adults by Euwer and Sontheimer [64] and include absence of proximal muscle weakness and normal muscle enzymes for 2 years after presentation, while skin lesions and skin biopsy are typical. Thirty-nine cases of suspected amyopathic JDM were reported in a survey across North America, but 13 patients had abnormal tests suggesting very mild myositis and therefore were not considered truly amyopathic. The incidence of calcinosis was very low in this population of patients [65]. El-Azhary et al [66] conducted a survey investigating the progression of amyopathic dermatomyositis to myositis and associated malignancy in adults. Only 2 of the 25 patients who could be reached at follow-up developed muscle weakness within 5 years after diagnosis, but 5 patients developed malignancies. None of the seven pediatric patients in this study had progression to myopathy.

## **Outcome measures**

To follow patients in the clinic and to compare patients in clinical studies, it is helpful to use accurate and reliable outcome measurement tools. The Juvenile Dermatomyositis Disease Activity Collaborative Study Group, along with the International Myositis Assessment and Clinical Studies (IMACS) group, has worked to develop and validate new tools to assess disease activity and damage in JDM. The tools most currently used are the Childhood Health Assessment Questionnaire (CHAQ), Manual Muscle Testing (MMT), the Childhood Myositis Assessment Scale (CMAS), the physician and patient global assessment of disease and skin activity, the physician and patient global assessment of disease and skin damage, and the parent global assessment of disease severity.

MMT is a score that putatively assesses only muscle strength. Seven proximal and five distal muscle groups are assessed bilaterally using a defined scoring system. MMT has been shown to be a significant predictor of disease activity. The CMAS, a measure that incorporates function as well as strength, may be more informative than MMT [67].

The CHAQ was initially developed to measure physical function in children with arthritis. It is a 30-item parent- or self-reporting questionnaire that reflects

the child's (or parent's) perceptions of physical abilities or disabilities [68]. This score has undergone validation in JDM; the CHAQ has shown good construct validity and responsiveness [69,70].

The CMAS is a 14-activity observational, performance-based assessment of physical function, strength, and endurance. It has been recently validated in JIIM and has been shown to be a valid assessment of muscle outcome [67,71]. The CMAS9, which includes nine CMAS maneuvers, has been evaluated in normal, healthy children between 4 and 9 years of age to generate normative data. These sex- and age-related normative data provide important information in the interpretation of the CMAS in children with JIIM [72].

Two different groups have recently proposed core sets of measures for disease activity and damage assessment in JDM. The goal of this work is to provide the clinician with standardized outcome measurements for use in clinical practice and in studies. Although MRI is widely used to assess disease activity and damage, it is not always easily available, so the core sets do not require imaging. The proposed core sets are summarized in Table 5 [73–75].

A growth and development domain has been added to the damage core set to assess growth retardation and delayed puberty. These areas are thought to be complications of chronic disease in many children. Candidate tools, including physician global damage assessments and CHAQ, have been proposed along with T1-weighted MRI to evaluate muscle damage and a cutaneous assessment

Table 5  
Juvenile dermatomyositis disease activity core set

Domain	Item used to measure the domain	
	PRINTO/PRCSG	IMACS
Global assessment by physicians	VAS or Likert scale	VAS or Likert scale
Muscle strength assessment	CMAS and MMT	MMT
Laboratory assessment: muscle enzymes	Creatinine phosphokinase, LDH, aldolase, AST/ALT	At least two of the following: creatinine phosphokinase, aldolase, LDH, AST/ALT
Functional ability assessment	CHAQ	CHAQ and CMAS
Global assessment by parents/patients	VAS or Likert scale	VAS or Likert scale
Global juvenile dermatomyositis disease activity tool	Disease activity score (DAS) and myositis disease activity assessment (MDAA)	

*Abbreviations:* CHAQ, Childhood Health Assessment Questionnaire; CMAS, Childhood Myositis Assessment Scale; LDH, lactate dehydrogenase; MMT, Manual Muscle Testing; PRCSG, Pediatric Rheumatology Collaborative Study Group (PRCSG); PRINTO, Pediatric International Trials Organization; VAS, visual analogue scale.

*From* Ruperto N, Ravelli A, Murray KJ, et al. Preliminary core sets of measures for disease activity and damage assessment in juvenile systemic lupus erythematosus and juvenile dermatomyositis. *Rheumatol* 2003;42:1452–9; with permission (PRINTO/PRCSG); Miller FW, Rider LG, Chung YL, et al. Proposed preliminary core set measures for disease outcome assessment in adult and juvenile idiopathic inflammatory myopathies. *Rheumatology (Oxford)* 2001;40(11):1262–73 (IMACS).

Table 6  
Juvenile dermatomyositis disease damage core set

Domain of damage	Item used to measure domain
Global assessment by physician	VAS or Likert scale
Functional ability assessment	CHAQ
Growth and development	Height and weight Menses Tanner puberty stage
Global JDM damage tool	Myositis Damage Index (MDI)
Muscle strength assessment	CMAS

*Abbreviations:* CHAQ, Childhood Health Assessment Questionnaire; CMAS, Childhood Myositis Assessment Scale; JDM, juvenile dermatomyositis; VAS, visual analog scale.

tool able to evaluate skin damage [75]. The core set proposed by Ruperto et al [73] is summarized in Table 6.

## Therapy

Kathryn was treated with MTX and oral and, later, intravenous corticosteroids. What are the best therapies for children with JIIM? Is the oral or intravenous route of corticosteroids better? What other agents are available for these disorders?

Corticosteroids have been the traditional mainstay of therapy for the JIIM; onset is rapid, and clinical efficacy is seen within days to weeks. Toxicity with chronic use of corticosteroids is high, however. MTX seems to work well in JIIM, especially at maintaining remission, but the onset is slow: MTX may take as long as 12 weeks before a clinical effect is seen. The approach at the Hospital for Sick Children has been to start treatment with corticosteroids and MTX together in patients with JIIM and to use the MTX to allow a much more rapid withdrawal of corticosteroids than had been traditionally done in the past.

Worldwide, corticosteroids remain the main medication used in the treatment of inflammatory myopathy. The authors initially use high-dose oral corticosteroids and subsequently adjust the treatment to the clinical response of the patient. They generally start a new patient with 2 mg/kg/day of prednisone divided into three equal doses (maximum daily dose rarely to exceed 80 mg). At 6 weeks, when clinical improvement is seen in strength, rash is improving, and muscle enzyme tests have normalized, they consolidate the prednisone into a twice-daily, and shortly afterwards a single-daily dose. The prednisone is then tapered by about 10% every 2 weeks.

In the case of incomplete or absent response (steroid resistance), intravenous methylprednisolone pulses (IVMP) (30 mg/kg per treatment, maximum 1000 mg)

are given to gain a rapid control of the systemic inflammation. In the presence of dysphagia and dysphonia, pulmonary disease, or suspected gastrointestinal vasculopathy, IVMP is often the initial treatment.

Several groups have proposed the use of IVMP in combination with daily oral corticosteroids for all patients [48,76,77]. The rationale is to achieve early remission to allow the daily oral corticosteroid dose to be decreased sooner and to prevent the side effects of long-term corticosteroid use and the complications related to prolonged disease activity, such as calcinosis. A group at Northwestern University conducted a cost-identification and cost-effectiveness analysis to compare oral and intermittent high-dose corticosteroids [78]. The investigators compared two groups of five patients: patients treated with oral corticosteroids (2 mg/kg/day) and patients who received intermittent IVMP along with low-dose daily oral corticosteroids (0.5 mg/kg/day). Patients treated with IVMP achieved a remission at a median of 2 years earlier, suggesting to the investigators that this approach is cost-effective. IVMP exposes the patient to possible adverse reactions, however [79].

Despite the excellent response to corticosteroids in this condition, the risk that long-term corticosteroid use may lead to growth retardation, cataracts, and secondary osteoporosis has resulted in the more widespread use of steroid-sparing agents.

MTX was first proposed as a second-line agent for refractory JDM along with corticosteroids [80]. It is now more widely prescribed early as a steroid-sparing agent. Treatment combining high-dose corticosteroids and MTX started within 4 weeks after the beginning of treatment in the absence of improvement in muscle enzymes may decrease the incidence of long-term complications such as calcinosis [49]. In a 12-patient pilot study, treatment with oral MTX in combination with intermittent IVMP was started within 6 weeks after diagnosis in six children. This group of patients improved clinically, and the oral corticosteroid dose could be decreased in five patients. None of these patients developed calcinosis. The results of this small study suggest that early use of MTX in combination with IVMP may be useful in JDM [81]. The authors have reported their use of MTX as a first-line treatment for JDM along with corticosteroids in 31 children and compared the clinical course and outcome with that of a control group treated primarily with corticosteroids. The two groups had similar clinical improvement, but the study group had much less exposure to corticosteroids because of an aggressive taper and a lower cumulative dose. The patients in the study group experienced fewer side effects with a greater height velocity and smaller weight gain [82]. Early use of MTX seems to be a safe and efficacious strategy.

Not all patients respond to the combination of MTX and corticosteroids. In some cases, the disease is so severe that additional agents are needed at the outset. In other cases, there is an early response but an inability to taper therapy. A number of additional agents have been proposed for use in JDM. The authors' practice has been to use intravenous immunoglobulin (IVIG) in both of these clinical settings. Very severe initial disease with severe vasculopathy (lungs, skin,

or gastrointestinal or nervous system) probably warrants more aggressive immunosuppression with cyclophosphamide.

Many groups have used IVIG with an apparently good response. The IVIG in these reports was given for different indications, including relapse, incomplete response, or for steroid-sparing purposes. The dose, the number of courses, and the time interval varied greatly among the different studies published [83–85]. Only one controlled trial (with adult patients) has conclusively demonstrated efficacy: 15 adult patients were treated with monthly infusions of IVIG for 3 months and improved objectively in strength, neuromuscular symptoms, skin rash, and histopathologic findings [86]. It is difficult to draw definite conclusions about the efficacy of IVIG, because the series published so far are small ( $\leq 18$  patients), and almost all the patients continued to receive corticosteroids along with another second-line agent, such as azathioprine, MTX, or cyclophosphamide, concomitantly. The authors' protocol has been to start treatment with IVIG at a dose of 2 g/kg per infusion (up to a maximum of 70 g) given every 2 weeks for five infusions. If this treatment is associated with clinical improvement, IVIG treatment continues monthly for up to a year. After 12 months of infusion, the authors taper the medication by lengthening the interval between infusions to 6 weeks, 8 weeks, and then to 12 weeks. Patients who can tolerate infusions spaced 12 weeks apart seem to be able to discontinue the therapy completely without flare of symptoms.

Cyclophosphamide has been used in severe and refractory JDM. In the authors' experience, the existence of prominent vasculopathic features such as skin ulcers may be an indication for monthly cyclophosphamide infusions. Twelve patients treated this way have been reported recently. They had refractory disease, and two of them died shortly after the first infusion of cyclophosphamide. The 10 remaining patients had a significant improvement in muscle function at 6 months of therapy without any serious short-term toxicity [87].

Other medications that have been used in treating JIIM include cyclosporin A [88–90] and hydroxychloroquine [91]. There is little published evidence to support either of these treatments. In the authors' experience, cyclosporine seems to be effective, but its use is often complicated by hypertension and hirsutism. Their patients have not seemed to respond noticeably to hydroxychloroquine. Topical FK506 (tacrolimus 0.1% ointment) has been tried in adult patients with refractory skin disease with a reported substantial benefit [92–94]. Therefore, topical tacrolimus seems to be an attractive adjunct given the good safety data in children [95].

### **Clinical outcome**

Kathryn is currently doing well, but what is her future prognosis? What will her school and work experience be? How long will she have her disease?

A few studies have reported the medium- and long-term functional outcomes of patients with JDM [40,45,50,96,97]. Bowyer et al [50] have reported that delayed treatment leads to poorer outcome in terms of disease course and calcinosis. Huber et al [97] looked at the outcomes of patients with JDM in an inception cohort using validated tools. These children were diagnosed between 1984 and 1994 at four Canadian pediatric referral centers with a median follow-up period of 7.2 years. The median age at follow-up was 13 years. Sixty-five of 80 patients could be contacted. Most of the patients had no delay in the initiation of their treatment. Thirty-seven percent of the patients had a monocyclic course (disease that went into permanent remission after about 2 years of activity); the remaining 63% had a chronic continuous or polycyclic course. Physical function was assessed using the CHAQ score. More than two thirds of the patients had a CHAQ score of 0, suggesting no or minimal disability, and only 8% had a score higher than 1.0, representing moderate to severe disability. The predictive factors of higher (worse) CHAQ scores were female gender, chronic continuous course, and presence of calcinosis at some point during the disease course. Growth was analyzed by predicting height based on the mid-parental height. Twenty patients (31%) were more than 1 SD below their predicted height, and 10 (16%) were more than 2 SD below their predicted height. In terms of educational and vocational achievement, some of the patients had failed a single grade because of disease-related absences from school, but they all seemed to have caught up academically. None of the patients had the impression that their disease had interfered with their ability to work. Calcinosis was observed in 22 patients (34%). In those patients, calcinosis developed a median 3.41 years after disease onset. No predictive factors were found for the development of calcinosis in this cohort [97]. At the time of follow-up, 40% of the patients continued to have a rash, and 23% reported weakness. Most of the patients had no pain, but children with a chronic continuous course had higher pain scores. About one third of the patients continued to take medications. In terms of comorbidity and mortality, three patients developed diabetes, and two developed an additional connective tissue disease (one with scleroderma and one with an overlap syndrome) after achieving remission of their JDM. No malignancy was reported. One patient died of acute myocardial failure secondary to multiple myocardial infarctions [61]. This recent study shows that the prognosis and outcome of JDM seem to be good. Patients with a chronic continuous course, however, have a significant long-term functional impairment and more frequently develop side effects of the therapy.

As demonstrated by Kathryn's case, JIIM are rare conditions that require somewhat aggressive anti-inflammatory and immunosuppressive therapy. JDM is by far the most common presentation, with most of the manifestations limited to skin and muscle. Rarely, however, any system can be involved by the underlying vasculopathy. The disorders have a good functional outcome, but many of the affected children will have chronic disease and will require long-term therapy. The outlook for Kathryn and other children with JIIM is bright. The recently expanded understanding of the genetic and immunopathologic under-

pinnings of the JIIM may result soon in improved, targeted therapies and an even better prognosis.

## References

- [1] Bohan A, Peter JB. Polymyositis and dermatomyositis [part 1 of 2]. *N Engl J Med* 1975; 292(7):34–7.
- [2] Banker BQ, Victor M. Dermatomyositis (systemic angiopathy) of childhood. *Medicine (Baltimore)* 1966;45(4):261–89.
- [3] Symmons DPM, Sills JA, Davis SM. The incidence of juvenile dermatomyositis: results from a nation-wide study. *Br J Rheumatol* 1995;34:732–6.
- [4] Mendez EP, Lipton R, Ramsey-Goldman R, et al. US incidence of juvenile dermatomyositis, 1995–1998: results from the National Institute of Arthritis and Musculoskeletal and Skin Diseases Registry. *Arthritis Rheum* 2003;49(3):300–5.
- [5] Medsger TAJ, Dawson WN, Masi AT. The epidemiology of polymyositis. *Am J Med* 1970;48: 715–23.
- [6] Ang P, Sugeng MW, Chua SH. Classical and amyopathic dermatomyositis seen at the national centre of Singapore: a 3-year retrospective review of their clinical characteristics and association with malignancy. *Ann Acad Med Singapore* 2000;29(2):219–23.
- [7] Pachman LM. Juvenile dermatomyositis: immunogenetics, pathophysiology and disease expression. *Rheum Dis Clin North Am* 2002;28:579–602.
- [8] Cassidy JT, Petty RE, editors. Juvenile dermatomyositis. In: *Textbook of pediatric rheumatology*. 4th edition. p. 465–504.
- [9] Reed AM, Stirling JD. Association of the HLA-DQA1\*0501 allele in multiple racial groups with juvenile dermatomyositis. *Hum Immunol* 1995;44:131–5.
- [10] Shamim EA, Rider LG, Miller FW. Update on the genetics of the idiopathic inflammatory myopathies. *Curr Opin Rheumatol* 2000;12:482–91.
- [11] West JE, Reed AM. Analysis of HLA-DM polymorphism in juvenile dermatomyositis (JDM) patients. *Hum Immunol* 1999;60:255–8.
- [12] Artlett CM, Ramos R, Jimenez SA, et al. Chimeric cells of maternal origin in juvenile idiopathic inflammatory myopathies. Childhood Myositis Heterogeneity Collaborative Group. *Lancet* 2000;356(9248):2155–6.
- [13] Artlett CM, Miller FW, Rider LG. Persistent maternally derived peripheral microchimerism is associated with the juvenile idiopathic inflammatory myopathies. *Rheumatology (Oxford)* 2001;40(11):1279–84.
- [14] Reed AM, Picornell YJ, Harwood A, et al. Chimerism in children with juvenile dermatomyositis. *Lancet* 2000;356:2156–7.
- [15] Reed AM, McNallan K, Wettstein P, et al. Does HLA-dependent chimerism underlie the pathogenesis of juvenile dermatomyositis. *J Immunol* 2004;172:5041–6.
- [16] Artlett CM, O'Hanlon TP, Lopez AM, et al. HLA-DQA1 is not an apparent risk factor for microchimerism in patients with various autoimmune diseases and in healthy individuals. *Arthritis Rheum* 2003;48(9):2567–72.
- [17] Verweij CL, Huizinga TWJ. Tumor necrosis factor alpha gene polymorphisms and rheumatic diseases. *Br J Rheumatol* 1998;37:923–9.
- [18] Wilson AG, de Vries N, Pociot F, et al. An allelic polymorphism within the human tumor necrosis factor alpha promoter region is strongly associated with HLA A1, B8, and DR3 alleles. *J Exp Med* 1993;177:557–60.
- [19] Wilson AG, Symons JA, McDowell TL, et al. Effects of a polymorphism in the human tumor necrosis factor alpha promoter on transcriptional activation. *Proc Natl Acad Sci U S A* 1997;94: 3195–9.
- [20] Pachman LM, Liotta-Davis MR, Hong DK, et al. TNFalpha-308A allele in juvenile

- dermatomyositis: association with increased production of tumor necrosis factor alpha, disease duration, and pathologic calcifications. *Arthritis Rheum* 2000;43(10):2368–77.
- [21] Fedczyna TO, Lutz J, Pachman LM. Expression of TNFalpha by muscle fibers in biopsies from children with untreated juvenile dermatomyositis: association with the TNFalpha-308A allele. *Clin Immunol* 2001;100(2):236–9.
- [22] Lutz J, Huwiler KG, Fedczyna T, et al. Increased plasma thrombospondin-1 (TSP-1) levels are associated with the TNF alpha-308A allele in children with juvenile dermatomyositis. *Clin Immunol* 2002;103:260–3.
- [23] Rider LG, Miller FW. Classification and treatment of the juvenile idiopathic inflammatory myopathies. *Rheum Dis Clin North Am* 1997;23(3):619–55.
- [24] Massa M, Costouros N, Mazzoli F, et al. Self epitopes shared between human myosin and *Streptococcus pyogenes* M5 protein are targets of immune responses in active juvenile dermatomyositis. *Arthritis Rheum* 2002;46(11):3015–25.
- [25] Tezak Z, Hoffman EP, Lutz JL, et al. Gene expression profiling in DQA1\*0501 + children with untreated dermatomyositis: a novel model of pathogenesis. *J Immunol* 2002;168(8):4154–63.
- [26] Wargula JC. Update on juvenile dermatomyositis: new advances in understanding its etiopathogenesis. *Curr Opin Rheumatol* 2003;15(5):595–601.
- [27] Goncalves FGP, Chimelli L, Sallum ME, et al. Immunohistological analysis of CD59 and membrane attack complex of complement in muscle in juvenile dermatomyositis. *J Rheumatol* 2002;29:1301–7.
- [28] Sallum AM, Marie SK, Wakamatsu A, et al. Immunohistochemical analysis of adhesion molecule expression on muscle biopsy specimens from patients with juvenile dermatomyositis. *J Rheumatol* 2004;31(4):801–7.
- [29] Li CKC, Varsani H, Holton JL, et al. MHC class I overexpression on muscles in early juvenile dermatomyositis. *J Rheumatol* 2004;31(3):605–9.
- [30] Bohan A, Peter JB. Polymyositis and dermatomyositis [part 2 of 2]. *N Engl J Med* 1975;292(8):403–7.
- [31] Feldman BM, Reichlin M, Laxer RM, et al. Clinical significance of specific autoantibodies in juvenile dermatomyositis. *J Rheumatol* 1996;23(10):1794–7.
- [32] Kimball AB, Summers RM, Turner M, et al. Magnetic resonance imaging detection of occult skin and subcutaneous abnormalities in juvenile dermatomyositis. *Arthritis Rheum* 2000;43(8):1866–73.
- [33] Maillard SM, Jones R, Owens C, et al. Quantitative assessment of MRI T2 relaxation time of thigh muscles in juvenile dermatomyositis. *Rheumatology* 2004;43(5):603–8.
- [34] Pachman LM, Hayford JR, Chung A, et al. Juvenile dermatomyositis at diagnosis: clinical characteristics of 79 children. *J Rheumatol* 1998;25(6):1198–204.
- [35] Pachman LM. Juvenile dermatomyositis. Pathophysiology and disease expression. *Pediatr Clin North Am* 1995;42(5):1071–98.
- [36] Miller LC, Michael AF, Kim Y. Childhood dermatomyositis: clinical course and long-term follow-up. *Clin Pediatr* 1987;26:561–6.
- [37] Tse S, Lubelsky S, Gordon M, et al. The arthritis of inflammatory childhood myositis syndromes. *J Rheumatol* 2001;28(1):192–7.
- [38] Hollister JR. The evolution of juvenile dermatomyositis into chronic arthritis. *Arthritis Rheum* 1998;41(Suppl):S203.
- [39] Ramanan AV, Feldman BM. Clinical features and outcomes of juvenile dermatomyositis and other childhood onset myositis syndromes. *Rheum Dis Clin North Am* 2002;28(4):833–57.
- [40] Peloro TM, Miller OF, Hahn TF, et al. Juvenile dermatomyositis: a retrospective review of a 30-year experience. *J Am Acad Dermatol* 2001;45(1):28–34.
- [41] Santmyire-Rosenberger B, Dugan EM. Skin involvement in dermatomyositis. *Curr Opin Rheumatol* 2003;15(6):714–22.
- [42] Ghali FE, Stein LD, Fine J, et al. Gingival telangiectases. An underappreciated physical sign of juvenile dermatomyositis. *Arch Dermatol* 1999;135:1370–4.

- [43] Feldman BM, Rider LG, Dugan L, et al. Nailfold capillaries as indicators of disease activity in juvenile idiopathic inflammatory myopathies (JIIM). *Arthritis Rheum* 1999;42(9):S181.
- [44] Smith RL, Sundberg J, Shamiyah E, et al. Skin involvement in juvenile dermatomyositis is associated with loss of end row nailfold capillary loops. *J Rheumatol* 2004;31(8):1644–9.
- [45] Ramanan AV, Feldman BM. Clinical outcomes in juvenile dermatomyositis. *Curr Opin Rheumatol* 2002;14(6):658–62.
- [46] Eddy MC, Leelawattana R, McAlister WH, et al. Calcinosis universalis complicating juvenile dermatomyositis: resolution during Probenecid therapy. *J Clin Endocrinol Metab* 1997;82(11):3536–42.
- [47] Ansell BM. Juvenile dermatomyositis. *Rheum Dis Clin North Am* 1991;17:931–42.
- [48] Pachman LM, Callen AM, Hayford J, et al. Juvenile dermatomyositis: decreased calcinosis with intermittent high-dose intravenous methylprednisolone (IV pulse). *Arthritis Rheum* 1994;37(Suppl 9):S429.
- [49] Fisler RE, Liang MG, Fuhlbrigge RC, et al. Aggressive management of juvenile dermatomyositis results in improved outcome and decreased incidence of calcinosis. *J Am Acad Dermatol* 2002;47:505–11.
- [50] Bowyer SL, Blane CE, Sullivan DB, et al. Childhood dermatomyositis: factors predicting functional outcome and development of dystrophic calcification. *J Pediatr* 1983;103:882–8.
- [51] Huemer C, Kitson H, Malleson PN, et al. Lipodystrophy in patients with juvenile dermatomyositis-evaluation of clinical and metabolic abnormalities. *J Rheumatol* 2001;28(3):610–5.
- [52] Senior B, Gellis SS. The syndromes of total lipodystrophy and partial lipodystrophy. *Pediatrics* 1964;33:593–612.
- [53] Trapani S, Camiciottoli G, Vierucci A, et al. Pulmonary involvement in juvenile dermatomyositis: a two-year longitudinal study. *Rheumatol* 2001;40:216–20.
- [54] Pachman LM, Cooke N. Juvenile dermatomyositis: a clinical and immunologic study. *J Pediatr* 1980;96(2):226–34.
- [55] Rider LG, Miller FW, Targoff IN. Myositis specific autoantibodies (MSA) in children: a broadened spectrum of juvenile myositis. *Arthritis Rheum* 1993;36:S258.
- [56] Fortenberry JD, Shew ML. Fatal *Pneumocystis carinii* in an adolescent with systemic lupus erythematosus. *J Adolesc Health Care* 1989;10(6):570–2.
- [57] Elst EF, Kamphuis SSM, Prakken BJ, et al. Severe central nervous system involvement in juvenile dermatomyositis. *J Rheumatol* 2003;30(9):2059–63.
- [58] Ramanan AV, Sawhney S, Murray KJ. Central nervous system complications in two cases of juvenile onset dermatomyositis. *Rheumatology (Oxford)* 2001;40(11):1293–8.
- [59] Regan M, Haque U, Pomper M, et al. Central nervous system vasculitis as a complication of refractory dermatomyositis. *J Rheumatol* 2001;28:207–11.
- [60] Askari AD, Huettner TL. Cardiac abnormalities in polymyositis/dermatomyositis. *Semin Arthritis Rheum* 1982;12(2):208–19.
- [61] Jimenez C, Rowe PC, Keene D. Cardiac and central nervous system vasculitis in a child with dermatomyositis. *J Child Neurol* 1994;9(3):297–300.
- [62] Bitnum S, Daeschner CWJ, Travis LB. Dermatomyositis. *J Pediatr* 1964;64:101–31.
- [63] Haupt HM, Hutchins GM. The heart and cardiac conduction system in polymyositis-dermatomyositis: a clinicopathologic study of 16 autopsied patients. *Am J Cardiol* 1982;50(5):998–1006.
- [64] Euwer RL, Sontheimer RD. Amyopathic dermatomyositis: a review. *J Invest Dermatol* 1993;100(1):124S–7S.
- [65] Plamondon S, Dent PB. Juvenile amyopathic dermatomyositis: results of a case finding descriptive survey. *J Rheumatol* 2000;27(8):2031–4.
- [66] El-Azhary RA, Pakzad SY. Amyopathic dermatomyositis: retrospective review of 37 cases. *J Am Acad Dermatol* 2002;46(4):560–5.
- [67] Huber AM, Feldman BM, Rennebohm RM, et al. Validation and clinical significance of the Childhood Myositis Assessment Scale for assessment of muscle function in the juvenile idiopathic inflammatory myopathies. *Arthritis Rheum* 2004;50(5):1595–603.

- [68] Singh G, Athreya BH, Fries JF, Goldsmith DP. Measurement of health status in children with juvenile rheumatoid arthritis. *Arthritis Rheum* 1994;37:1761–9.
- [69] Feldman BM, Ayling-Campos A, Luy L, et al. Measuring disability in juvenile dermatomyositis: validity of the childhood health assessment questionnaire. *J Rheumatol* 1995;22(2):326–31.
- [70] Huber AM, Hicks JE, Lachenbruch PA, et al. Validation of the Childhood Health Assessment Questionnaire in the juvenile idiopathic myopathies. Juvenile Dermatomyositis Disease Activity Collaborative Study Group. *J Rheumatol* 2001;28(5):1106–11.
- [71] Lovell DJ, Lindsley CB, Rennebohm RM, et al. Development of validated disease activity and damage indices for the juvenile idiopathic inflammatory myopathies. II. The Childhood Myositis Assessment Scale (CMAS): a quantitative tool for the evaluation of muscle function. The Juvenile Dermatomyositis Disease Activity Collaborative Study Group. *Arthritis Rheum* 1999;42(10):2213–9.
- [72] Rennebohm RM, Jones K, Huber AM, et al. Normal scores for nine maneuvers of the Childhood Myositis Assessment Scale. *Arthritis Rheum* 2004;51(3):365–70.
- [73] Ruperto N, Ravelli A, Murray KJ, et al. Preliminary core sets of measures for disease activity and damage assessment in juvenile systemic lupus erythematosus and juvenile dermatomyositis. *Rheumatol* 2003;42:1452–9.
- [74] Isenberg DA, Allen E, Farewell V, et al. International consensus outcome measures for patients with idiopathic inflammatory myopathies. Development and initial indices in patients with adult onset disease. *Rheumatol* 2004;43:49–54.
- [75] Miller FW, Rider LG, Chung YL, et al. Proposed preliminary core set measures for disease outcome assessment in adult and juvenile idiopathic inflammatory myopathies. *Rheumatology (Oxford)* 2001;40(11):1262–73.
- [76] Laxer RM, Stein LD, Petty RE. Intravenous pulse methylprednisolone treatment of juvenile dermatomyositis. *Arthritis Rheum* 1987;30(3):328–34.
- [77] Paller AS. The use of pulse corticosteroid therapy for juvenile dermatomyositis. *Pediatr Dermatol* 1996;13(4):347–8.
- [78] Klein-Gitelman MS, Waters T, Pachman LM. The economic impact of intermittent high-dose intravenous versus oral corticosteroid treatment of juvenile dermatomyositis. *Arthritis Care Res* 2000;13(6):360–8.
- [79] Klein-Gitelman MS, Pachman LM. Intravenous corticosteroids (IV CS): adverse reactions are more variable than expected in children. *J Rheumatol* 1998;25:1995–2002.
- [80] Miller LC, Sisson BA, Tucker LB, et al. Methotrexate treatment of recalcitrant childhood dermatomyositis. *Arthritis Rheum* 1992;35(10):1143–9.
- [81] Al-Mayouf S, Al-Mazyed A, Bahabri S. Efficacy of early treatment of severe juvenile dermatomyositis with intravenous methylprednisolone and methotrexate. *Clin Rheumatol* 2000;19:138–41.
- [82] Ramanan A, Campbell-Webster N, Tran D, et al. Initial treatment of juvenile dermatomyositis (JDM) using methotrexate (MTX) and aggressively tapered prednisone (PRED). *Pediatric Rheumatology Online Journal*;1(4):120. Available at <http://www.pedrheumonlinejournal.org/July/derm/123.htm>. Accessed February 8, 2005.
- [83] Al-Mayouf SM, Laxer RM, Schneider R, et al. Intravenous immunoglobulin therapy for juvenile dermatomyositis: efficacy and safety. *J Rheumatol* 2000;27(10):2498–503.
- [84] Sansome A, Dubowitz V. Intravenous immunoglobulin in juvenile dermatomyositis—four year review of nine cases. *Arch Dis Child* 1995;72:25–8.
- [85] Lang B, Murphy G. Treatment of dermatomyositis with intravenous globulin. *Am J Med* 1991;91:169–72.
- [86] Dalakas MC, Illa I, Dambrosia JM, et al. A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. *N Engl J Med* 1993;329(27):1993–2000.
- [87] Riley P, Maillard SM, Wedderburn LR, et al. Intravenous cyclophosphamide pulse therapy in juvenile dermatomyositis. A review of efficacy and safety. *Rheumatol* 2004;43(4):491–6.
- [88] Heckmatt J, Hasson N, Saunders C, et al. Cyclosporin in juvenile dermatomyositis. *Lancet* 1989;1063–6.

- [89] Zeller V, Cohen P, Prieur A, et al. Cyclosporin A therapy in refractory juvenile dermatomyositis. Experience and longterm followup of 6 cases. *J Rheumatol* 1996;23(8):1424–7.
- [90] Kobayashi I, Yamada M, Takahashi Y, et al. Interstitial lung disease associated with juvenile dermatomyositis: clinical features and efficacy of cyclosporin A. *Rheumatology (Oxford)* 2003;42(2):371–4.
- [91] Olson NY, Lindsley CB. Adjunctive use of hydroxychloroquine in childhood dermatomyositis. *J Rheumatol* 1989;16(12):1545–7.
- [92] Yoshimasu T, Ohtani T, Sakamoto T, et al. Topical FK506 (tacrolimus) therapy for facial erythematous lesions of cutaneous lupus erythematosus and dermatomyositis. *Eur J Dermatol* 2002;12:50–2.
- [93] Hollar CB, Jorizzo JL. Topical tacrolimus 0.1% ointment for refractory skin disease in dermatomyositis: a pilot study. *J Dermatolog Treat* 2004;15(1):35–9.
- [94] Ueda M, Makinodan R, Matsumura M, et al. Successful treatment of amyopathic dermatomyositis with topical tacrolimus. *Br J Dermatol* 2003;148:593–611.
- [95] Paller A, Eichenfield LF, Leung DYM. A 12-week study of tacrolimus ointment for the treatment of atopic dermatitis in pediatric patients. *J Am Acad Dermatol* 2001;44(1 Suppl): S47–57.
- [96] Shehata R, Al-Mayouf S, Al-Dalaan A, et al. Juvenile dermatomyositis: clinical profile and disease course in 25 patients. *Clin Exp Rheumatol* 1999;17(1):115–8.
- [97] Huber AM, Lang B, LeBlanc CMA, et al. Medium- and long-term functional outcomes in a multicenter cohort of children with juvenile dermatomyositis. *Arthritis Rheum* 2000;43(3): 541–9.