Collagen Vascular Diseases: SLE, Dermatomyositis, Scleroderma, and MCTD

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Practice Gap

Timely and accurate recognition of collagen vascular disorders (CVDs), and implementation of effective screening and referral processes for patients suspected of having a CVD, remain a challenge for many physicians. The result, too often, is unnecessary testing and referrals, and in some cases unnecessary anxiety for physicians, patients, and parents.

Objectives After completing this article, readers should be able to:

1. Recognize the common clinical symptoms and signs of systemic lupus erythematosus, dermatomyositis, and scleroderma, and their distinction from common infectious mimics.
2. Recognize the testing that can clarify the likelihood of whether a child has a rheumatic disease, including the limited utility of early serologic testing for autoantibodies.
3. Recognize the prognosis and management objectives for these often-chronic disorders, and practical steps to ensure excellent outcomes.

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ABBREVIATIONS

ANA	antinuclear antibody
CTD	connective tissue disease
CVD	collagen vascular disease
dsDNA	doubled-stranded DNA
DM	dermatomyositis
ENA	extractable nuclear antigen
JIA	juvenile idiopathic arthritis
MCTD	mixed connective tissue disease
NFC	nail fold capillary
RA	rheumatoid arthritis
RF	rheumatoid factor
RP	Raynaud phenomenon
RNP	ribonucleoprotein
SLE	systemic lupus erythematosus

INTRODUCTION

Timely and accurate recognition of collagen vascular diseases (CVDs), and implementation of effective screening and referral processes for patients suspected of having a CVD, remain challenging for many physicians. The result, too often, is unnecessary testing with questionable results, leading in some cases to unnecessary referrals and anxiety for physicians, patients, and parents. (1)

Sometimes, CVDs are also referred to as connective tissue diseases (CTDs), but neither name fully captures their essential nature. These are not primarily heritable disorders affecting collagen-containing structures, or disorders of vascular development, but rather are immune-mediated inflammatory diseases. The immunologic targets vary, but the inflammatory disease often affects collagen-containing tissues, including the musculoskeletal system and many other tissues. The targeting of blood vessels can lead to manifestations ranging from reversible vasospasm of Raynaud phenomenon (RP) to vascular injury of 1 or more organ systems, often with serious consequences.

The diseases that are classically included under the heading of CVDs/CTDs for adults include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren syndrome, dermatomyositis (DM) and polymyositis, scleroderma, mixed connective tissue disease (MCTD), and many forms of idiopathic vasculitis. For the purposes of this review, the focus will be on SLE, DM, and scleroderma, with mention also of RP and MCTD. Any references to RA are specific to the adult disease and the childhood equivalent termed "rheumatoid factor (RF)–positive juvenile idiopathic arthritis (JIA)." Due to past confusion over the relationship between a specific disease in adults termed "rheumatoid arthritis" and a group of diseases in children termed "juvenile rheumatoid arthritis," the preferred term for the group of diseases in children is now "juvenile idiopathic arthritis." Few children (<10%) with JIA have the childhood equivalent of RA.

CLINICAL APPROACH

The approach to rheumatic diseases is similar to that for other medical problems, namely, use of a thorough history and physical examination to help the clinician quickly identify the most likely diagnostic possibilities and focus diagnostic testing. The starting point is a general comprehensive health history and problem list, followed by a detailed history of any new medical concerns. The health history is followed by a comprehensive physical examination, with additional focus on the new medical concerns. A focused examination that accurately characterizes the abnormal findings of involved areas can greatly streamline the evaluation process.

On completion of a detailed and specific problem list based on the medical history and physical examination, the next steps in the evaluation and management become clearer. In some cases, no additional studies, such as imaging or laboratory tests, are needed. However, in the case of CVDs/CTDs, which are often complex in their manifestations, imaging and laboratory tests are commonly needed. Sometimes a quick phone consultation with a rheumatologist can actually simplify the process. Although this step might seem more time-consuming, a well-constructed and communicated diagnostic and treatment plan will help the physician, patient, and parents quickly feel confident that they are on the right path.

CASE EXAMPLE PART 1: INITIAL PRESENTATION

A previously well 10-year-old girl noted that, on exposure to the winter cold, her fingers would tingle and then blanch to white, recover to a bluish cold, and when rewarmed would become bright red and sting. This circulatory problem was less apparent as summer approached, but then she began having increased fatigue, shortness of breath with sports that was not improved with an inhaled bronchodilator, and an inability to fully extend her elbows. After the start of school in the fall she began having recurrent fevers and sore throats, but throat cultures were repeatedly negative. A scaly red rash appeared on her face and was partially responsive to topical glucocorticoid treatment. Her appetite unexpectedly dropped off and her weight plateaued.

On physical examination she had a distinctly erythematous and scaly rash on her cheeks, chin, and ears. Similar erythema and scale was present on the extensor side of the finger joints, mixed with scattered atrophic areas. She had a symmetrical polyarthritis affecting the elbows, wrists, fingers, knees, and toes. Features of the arthritis for many joints included swelling and loss of range of motion associated with pain at the limits of motion. The larger joints were unusually warm to the touch. Magnified inspection (with an otoscope or a dermatoscope) of the skin folds (eponychium) proximal to her fingernails showed that the nail fold capillaries (NFCs) were thickened and irregular. (2)

The diagnostic considerations for this patient are many, but the problem list quickly suggests a narrow list of possible CVDs/CTDs. This patient's problem list included the following:

- Fatigue, impaired activity level, impaired weight gain, shortness of breath, recurrent fever, and recurrent nonstreptococcal pharyngitis
- Digital vasospasm with abnormal NFCs
- Rashes of the face, ears, and hands with erythema, scale, and some atrophy
- Symmetrical polyarthritis

The first distinguishing feature for this child is her history of digital vasospasm associated with abnormal NFCs. Reversible vasospasm of distal arterial vessels is a feature of RP. This vasospasm is most commonly triggered by cold or other stresses, and it can occur as a primary process or as a secondary process associated with several CVDs/CTDs. Although classically defined as being triphasic, not all patients go through 3 discrete phases. (3) With vasospasm, the digit exhibits a distinctly demarcated distal pallor (Fig 1) and coolness, and then progresses through a cool dusky bluish phase and/or a bright hyperemic flush. Sensory changes, including pain and burning, may occur but are not always present during the phases of restricted blood flow and flushing.

Raynaud phenomenon is labeled as primary when it occurs in isolation or as secondary when it occurs in association with a

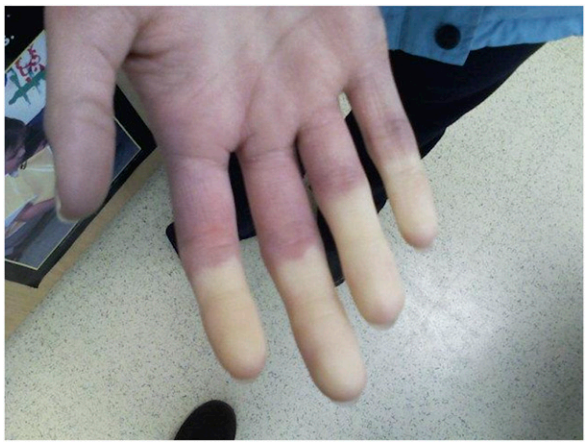

Figure 1. Raynaud phenomenon, ischemic phase, with an abrupt line of demarcation of nonperfused skin.

CVD/CTD. Secondary RP, but not primary RP, may feature distinctly abnormal NFCs. The capillaries are normally barely visible and fine in caliber as they extend to the end of the skin (Fig 2A), but with inflammatory vascular disease there may be progressive changes in the caliber and shape of the capillaries, including thickening, irregularity, and even occlusion with capillary dropout (Fig 2B). Primary RP is often confused with acrocyanosis, a condition in which individuals have constitutionally cool hands or feet. With acrocyanosis, the autonomic regulation of superficial blood flow leads the skin of the distal extremities to be naturally cool and dusky in color. With cold exposure the skin can become somewhat pale, but in contrast to RP there will not be a discretely demarcated distal pallor. Just as NFC changes are not a feature of primary RP, they are also not a feature of acrocyanosis. The CVDs/CTDs with which NFC changes are most common are SLE, DM, scleroderma, and MCTD.

The second distinguishing feature for this child is the prominent facial rash, for which some of the same diagnoses on this short list of CVDs/CTDs are the primary considerations. Let's further review each of these possibilities.

SYSTEMIC LUPUS ERYTHEMATOSUS

Definition

Systemic lupus erythematosus is commonly described as one of the clearest examples of autoimmunity that exhibits florid laboratory evidence of inappropriate immune activation and can cause damage to almost any part of the body, from head to toe. The variability of its manifestations is a source of much confusion, and any 2 individuals can differ vastly in the presentation and evolution of their disease.

Epidemiology

The epidemiology of SLE is still an area of active research, and estimates of its prevalence are highly variable, with an upper limit of approximately 1 million individuals in the United States with SLE. This disorder predominantly affects adults (80%–90%), predominantly females (≥90%), and is most common above age 10 years, but there are tremendous differences in prevalence and severity among different groups. On average it tends to be more common and more severe in its manifestations for nonwhite groups, including people of African, Asian, and Hispanic ancestry, and it is not unusual for there to be a family history of SLE.

Pathogenesis and Presentation

Systemic lupus erythematosus features activation of innate and adaptive immune systems, including humoral and cellular immunity. Interferon-α seems to be a key driver of this immune overactivity. Although a generalized hypergammaglobulinemia is common, overproduction of specific autoantibodies is nearly universal. Complement activation plays a major role in many of its manifestations, and depletion of serum levels of C3 and C4 is common during active disease. Deposits of complement components can be found on immunofluorescence studies of many affected tissues.

The presentation of SLE can be acute or insidious, initially affecting a single organ system or presenting with

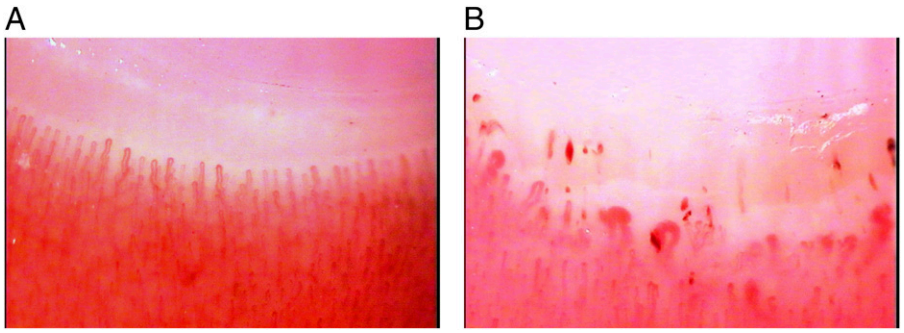

Figure 2. A. Normal fine nail fold capillaries as seen on capillary microscopy. (4) B. Abnormal nail fold capillaries, including microhemorrhages, dilated capillaries, megacapillaries, and avascular areas, as noted by the authors. (4)

multisystem disease, but often includes intrusive constitutional symptoms. The symptoms and signs can present asynchronously, and careful consideration of past and present problems helps with identification of SLE as a possible diagnosis that warrants further evaluation. Although the initial problem can even be relatively minor, such as a mild RP, children with SLE often have fast progression of worsening disease features and are commonly diagnosed within 6 to 12 months of onset of the original symptoms.

Since the spectrum of manifestations is so diverse, a good starting point for thinking about SLE is to consider the descriptors in the 1997 American College of Rheumatology classification criteria (Table 1) or the 2012 Systemic Lupus International Collaborating Clinics criteria (Table 2). Although these are not meant to be followed rigidly as diagnostic criteria, they are helpful for recognizing discriminating features of SLE; for focusing the review of the patient's medical history, physical

TABLE 1. **ACR Criteria for the Classification of SLE**

	CRITERION	DEFINITION
1	Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2	Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3	Photosensitivity	Skin rash as a result of an unusual reaction to sunlight, by patient history or physician observation
4	Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
5	Arthritis	Nonerosive arthritis involving ≥2 peripheral joints, characterized by tenderness, swelling, or effusion
6	Serositis	A. Pleuritis-convincing history of pleuritis pain or rub heard by a physician or evidence of pleural effusion OR B. Pericarditis documented by ECG or rub or evidence of pericardial effusion
7	Renal disorder	A. Persistent proteinuria >0.5 per day or >3+ if quantitation not performed OR B. Cellular casts, may be red blood cell, hemoglobin, granular, tubular, or mixed
8	Neurologic disorder	A. Seizures, in the absence of offending drugs or known metabolic derangements, eg, uremia, ketoacidosis, or electrolyte imbalance, OR B. Psychosis, in the absence of offending drugs or known metabolic derangements, eg, uremia, ketoacidosis, or electrolyte imbalance
9	Hematologic disorder	A. Hemolytic anemia, with reticulocytosis OR B. Leukopenia, <4,000/mm total on ≥2 occasions OR C. Lymphopenia, <1,500/mm on ≥2 occasions OR D. Thrombocytopenia, <100,000/mm in the absence of offending drugs
10	Immunologic disorder	A. Anti-DNA: antibody to native DNA in abnormal titer OR B. Anti-Sm: presence of antibody to Sm nuclear antigen OR C. Positive finding of antiphospholipid antibodies based on 1) an abnormal serum level of IgG or IgM anticardiolipin antibodies, 2) a positive test result for lupus anticoagulant using a standard method, or 3) a false-positive serologic test for syphilis known to be positive for ≥6 mo and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
11	Antinuclear antibody (ANA)	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any time and in the absence of drugs known to be associated with drug-induced lupus syndrome

The criteria are cumulative and need not be present concurrently. The patient may be classified as having SLE with 4 of 11 criteria. ACR=American College of Rheumatology, ECG=electrocardiography, IgG/IgM=immunoglobulin G/M, SLE=systemic lupus erythematosus.

Adapted with permission from Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. *1982;25(11):1271–1277 (5) and Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus.* Arthritis Rheum. *1997;40(9):1725. (6)*

TABLE 2. **SLICC Criteria for the Classification of SLE**

The criteria are cumulative and need not be present concurrently. A patient may be classified as having SLE with either:
1. Four of the clinical and immunologic criteria, including ≥1 clinical criterion and 1 immunologic criterion, or
2. Biopsy-proven nephritis compatible with SLE in the presence of ANAs or anti-dsDNA antibodies
Clinical criteria:
1. Acute cutaneous lupus, including lupus malar rash, bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash in the absence of dermatomyositis OR subacute cutaneous lupus
2. Chronic cutaneous lupus, including classic discoid rash, hypertrophic lupus, lupus panniculitis, mucosal lupus, lupus erythematosus tumidus, chilblains lupus, discoid lupus/lichen planus overlap
3. Oral ulcers OR nasal ulcers, in the absence of other causes
4. Nonscarring alopecia, in the absence of other causes
5. Synovitis involving ≥2 joints, characterized by swelling or effusion OR tenderness in and ≥30 min of morning stiffness
6. Serositis, including pleurisy for >1 d or pericarditis, in the absence of other causes
7. Renal disease, with a urine protein to creatinine ratio (or 24-h urine protein level) representing 500 mg protein/24 h OR red blood cell casts
8. Neurologic disease, including seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, or acute confusional state, in the absence of other causes
9. Hemolytic anemia
10. Leukopenia (<4,000/mm^3) OR lymphopenia (<1,000/mm^3), in the absence of other known causes
11. Thrombocytopenia (<100,000/mm^3), in the absence of other known causes
Immunologic criteria:
1. ANA screen positive
2. Anti-dsDNA antibody positive (≥2-fold if tested by ELISA)
3. Anti-Sm (Sm nuclear antigen) antibody positive
4. Antiphospholipid antibody positive as determined by any of the following: positive test result for lupus anticoagulant, false-positive test result for rapid plasma reagin, medium- or high-titer anticardiolipin antibody level (IgA, IgG, or IgM), positive test result for anti–β-2-glycoprotein I (IgA, IgG, or IgM)
5. Low complement test result, including C3, C4, or CH50
6. Direct Coombs test positive in the absence of hemolytic anemia

ANA=antinuclear antibody, dsDNA=double-stranded DNA, ELISA=enzyme-linked immunosorbent assay, IgA/G/M=immunoglobulin A/G/M, SLE=systemic lupus erythematosus, SLICC=Systemic Lupus International Collaborating Clinics.
Adapted with permission from Petri M, Orbai AM, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. *2012;64(8):2677–2686. (7)*

examination, and laboratory and imaging studies; and for planning next steps.

Symptoms and Signs

These criteria particularly highlight the mucocutaneous manifestations that affect 75% of patients, including the well-known malar rash that affects the cheeks and the bridge of the nose. This rash can have "discoid" features, including erythematous scaly and/or atrophic involvement. Many patients first learn that they have skin photosensitivity when rashes appear or dramatically worsen with sun exposure or when they develop new sunburns or blisters out of proportion to their sun exposure. Skin changes can also result from the vasculitic nature of SLE, including RP with NFC changes, purpuric lesions unexplained by local injury or coagulopathy, and scarring lesions (especially on the digits) due to tissue infarction.

Oral mucosal lesions are common and can be painful or painless (Fig 3). Hard palate lesions are often colorful but painless, but most other lesions are painful. A painful pharyngitis and prominent cervical adenopathy may develop such that the patient might be thought to have an infectious disease such as streptococcal pharyngitis or infectious mononucleosis.

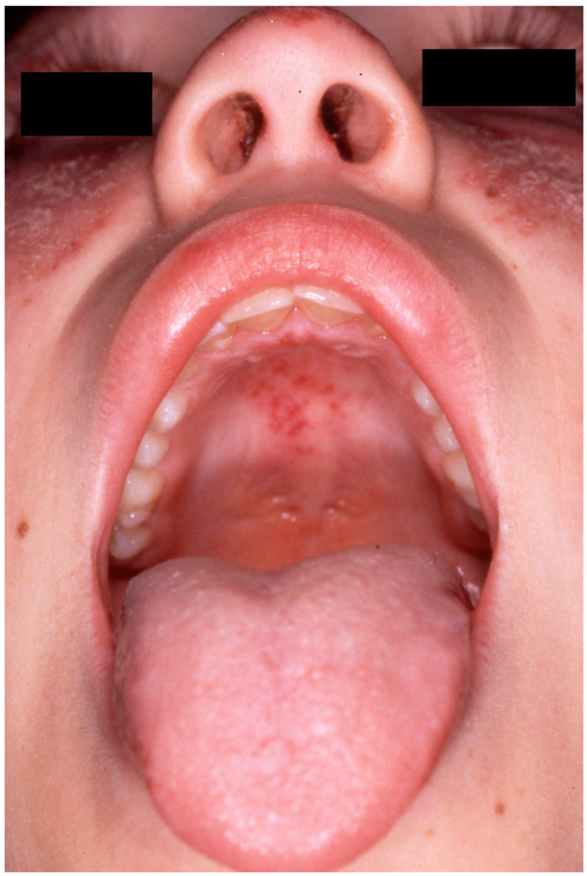

Figure 3. Systemic lupus erythematosus with scaly malar rash and punctate erythematous rash on the hard palate.

Most children with SLE have arthritis, but the degree and pattern of involvement is highly variable. Joints of the upper or lower extremities may be involved in a way that suggests severe RA and can even be associated with the presence of RF, but it is not common to see early radiographic damage typical of RA.

Renal disease with active urinary sediment (hematuria, proteinuria, casts), and cytopenias are seen in most patients as well, and serositis and neurologic symptoms are slightly less common.

For the patient described in the case presentation, SLE could explain every one of the features of her problem list, not just RP and facial rash.

Diagnostic Approach

In addition to a complete history and physical examination, the findings on a complete blood cell count and urinalysis with microscopy can quickly provide evidence supportive of the possibility of SLE.

The antinuclear antibody (ANA) screening test takes longer and is nearly always positive. However, given the high background frequency for this result in normal children (25%), it is also a major cause of unnecessary anxiety when it is ordered for a patient with a low previous probability of SLE. A positive ANA screen in the right clinical context leads to follow-up testing for SLE-specific ANAs, including anti–double-stranded DNA antibodies (anti-dsDNA) and anti-Smith antibody, and testing for complement consumption (low C_3 and C_4). In contrast, a negative screening ANA result is strong evidence against the possibility of SLE.

There should also be consideration of screening for the extent of organ involvement, such as serum creatinine and albumin levels to help judge the severity of the renal injury suggested by an abnormal urinalysis result. Similarly, a quick look at the American College of Rheumatology and Systemic Lupus International Collaborating Clinics criteria with the patient in mind might suggest other relevant next steps, such as chest radiography when there have been symptoms or signs suggestive of pleural or pericardial disease.

Despite continuing efforts to refine classification criteria for SLE, the diagnosis can at times still be complicated because many other infections (Epstein-Barr virus, parvovirus B19, human immunodeficiency virus), autoimmune diseases (MCTD, Henoch-Schonlein purpura, antineutrophil cytoplasmic antibody–associated vasculitis), and even malignancies (leukemia, lymphoma) can present with symptoms or signs that mimic SLE. The classification criteria cannot be applied without consideration of these other possibilities, and input from an experienced rheumatologist or nephrologist should be sought to confirm the diagnosis.

Management

The successful long-term management of SLE depends on accurate characterization of the extent and severity of organ involvement, and then tailoring of therapy based on the individual's needs.

In terms of the immediate management of an outpatient in your clinic, symptomatic treatment for the arthritis or serositis can be provided with acetaminophen or with a nonsteroidal anti-inflammatory drug if there are no renal concerns. Common topical therapies for the mucosal or skin manifestations can also be recommended for temporary relief until a more definitive therapy plan is in place. Antihypertensive therapy may be needed for the patient with renal disease.

A more definitive plan for therapy usually gets started only after full characterization of the patient's condition, and the plan is tailored to be appropriate for the extent of

involvement. This plan usually incorporates a combination of medications that have anti-inflammatory and/or immunosuppressive properties that reduce cytokine production, autoantibody production, complement activation, and infiltration of tissues by inflammatory cells.

Commonly used therapies include glucocorticoids, which provide fast-acting anti-inflammatory and immunosuppressive effects. With glucocorticoid therapy it is important to ensure adequate calcium and vitamin D intake and to consider needs for gastrointestinal protection. Nearly every patient with SLE will also receive hydroxychloroquine, which is anti-inflammatory and immune-stabilizing without causing immune suppression, and which can reduce the long-term need for glucocorticoids. Many patients require azathioprine, mycophenolate mofetil, or, in the most severe cases, cyclophosphamide, all of which suppress abnormal and normal immune function and can increase the risk of infections. Some of these therapies have significant implications regarding fertility or pregnancy, so counseling on these topics may be needed for both males and females. Newer therapies include belimumab and rituximab, biological molecules that target B lymphocytes. Reigning-in overactive B lymphocytes with these therapies is more commonly done for adult SLE; they are not Food and Drug Administration–approved therapies for childhood SLE.

The importance of the nonglucocorticoid therapies cannot be overstated, as it is now apparent that patients with SLE are living long and productive lives but having substantial morbidity attributable at least in part to their glucocorticoid treatment history, including accelerated atherosclerotic disease.

Prognosis and Follow-up

Although SLE can be immediately life-threatening, the most typical course is now that of a chronic disease with a persistent or relapsing course. With modern immunosuppressive and immunomodulatory therapies, a child is expected to have a long and productive life, but, unfortunately, the complexity and chronicity of the disease and its treatment can still result in substantial morbidity. It is important for there to be close collaboration between members of their primary clinic and the team specializing in SLE and the support of families, friends, and other community members to ensure the best quality of life and health.

DERMATOMYOSITIS

Definition

Dermatomyositis is an autoimmune disease featuring small vessel vasculopathy primarily affecting the skin and muscles, resulting in prominent rashes of the face and joints, and muscle weakness and fatigue that impair activities. It is sometimes complicated by significant involvement of other organ systems, especially the gastrointestinal and respiratory systems.

Epidemiology

Dermatomyositis affects both adults and children, and in children it primarily affects the school-aged group, although a substantial minority start earlier. Dermatomyositis is slightly more common in girls than in boys, but there are no major differences in its prevalence in children of different ancestry. The exact incidence and prevalence of childhood DM are not known, but its incidence is probably similar to that of SLE.

Pathogenesis and Presentation

As with other autoimmune disorders, the pathogenesis of DM seems to be multifactorial, with both genetic susceptibility and environmental triggers playing a role in its development. New cases are seen year-round, although seasonal variation of the rate of new cases has resulted in studies of infectious and environmental triggers. Certainly, the photosensitive nature of the disease can lead to flares or greater recognition during sunny times, but for most individuals, no triggering event will be apparent and no family history of another affected individual will be found.

Similar to other CTDs/CVDs, there are a variety of immunologic abnormalities evident in DM, including aberrant activity of the innate and adaptive immune systems. These abnormalities include activation of interferon-α pathways, autoantibody production, and inflammatory cellular infiltrates associated with a small vessel vasculopathy.

Symptoms and Signs

The symptoms and signs of DM reflect where the vasculopathy is most prominent, and the presentation and course for different patients can vary significantly. The clinical phenotype can sometimes be anticipated by the presence of particular "myositis-associated" or "myositis-specific" antibodies, but these associations are better characterized in adult populations than in childhood populations.

The typical patient with childhood DM presents with insidious onset of fatigue and fatigability with activities, often progressing to proximal muscle weakness that interferes with basic activities of daily living. Sometimes the onset can be acute, but it is not typically as abrupt as the myositis seen with viral illnesses such as influenza. The pattern of proximal muscle involvement is another feature that distinguishes it from acute viral myositis, which often causes distal injury such as painfully tender calf muscles.

The proximal weakness of DM leads to characteristic functional impacts, including difficulty getting on and off the floor, climbing stairs, climbing in and out of a vehicle, and even getting on and off the toilet independently. Upper extremity involvement leads to difficulty lifting objects with the arms, including difficulty getting items on and off elevated shelves, or even lifting the arms to do basic care activities such as combing hair. Neck muscle weakness can lead to difficulty with head control. In severe cases, pharyngeal muscle weakness leads to trouble with phonation and coordination of swallowing, and drinks can end up being misdirected out the nose or into the airway, resulting in aspiration. The child may even have trouble swallowing saliva without aspirating it. Respiratory symptoms can also develop due to profound respiratory muscle weakness or autoimmune lung disease of a variety of types.

On manual muscle testing, relatively symmetrical proximal muscle weakness may be detected. For a supine patient, trouble keeping the head off the table may be the most sensitive finding and indicates neck flexor weakness. Trouble lifting each leg indicates hip flexor weakness, and sit-ups test the hip flexors, abdominal muscles, and neck flexors. Trouble raising the arms while sitting upright tests the shoulder abductors. A nondeforming arthritis is not unusual, and both the arthritis and the myositis can contribute to contractures.

Before or after the onset of myositis, the patient will also have a dermatitis, which may have been overlooked or may have been prominent but not definitively recognized. In many cases, patients will report that they developed a sunburn, contact sensitivity, or unusual eczematous dermatitis that was unexpected in its onset, severity, or (lack of) improvement over time. On examination there is a typical distribution to the skin involvement. As with SLE, a prominent facial or malar dermatitis affecting the cheeks and the bridge of the nose is common, but there is also a distinctive involvement of the upper eyelids, with a violaceous color and sometimes edema (Fig 4A). This "heliotrope" rash is a pathognomonic feature of DM.

A scaly dermatitis with or without papules over the extensor surfaces of the finger metacarpophalangeal and proximal interphalangeal joints is commonplace, often with a mild streaky erythema between the joints (Fig 4B). The papules, known as Gottron papules, can seem like smooth, flat-topped warts and are nontender. A similarly scaly erythematous dermatitis can also occur over the extensor side of the elbows and knees and on the ankle malleoli. As with SLE, severe vascular injury can lead to infarcts of skin on the fingers or other areas, resulting in skin ulceration and calcium deposits (calcinosis) that can be confirmed with plain radiographs.

Striking changes to NFCs may be present, and because their condition is an indicator of the activity of microvascular disease, serial examination can be helpful for optimizing and monitoring medical therapy. The small vessel vasculopathy can also result in prominent gingival erythema evident on oral examination, but other oral lesions are uncommon.

Worrisome developments that may require emergency evaluation and possible hospitalization can include inability

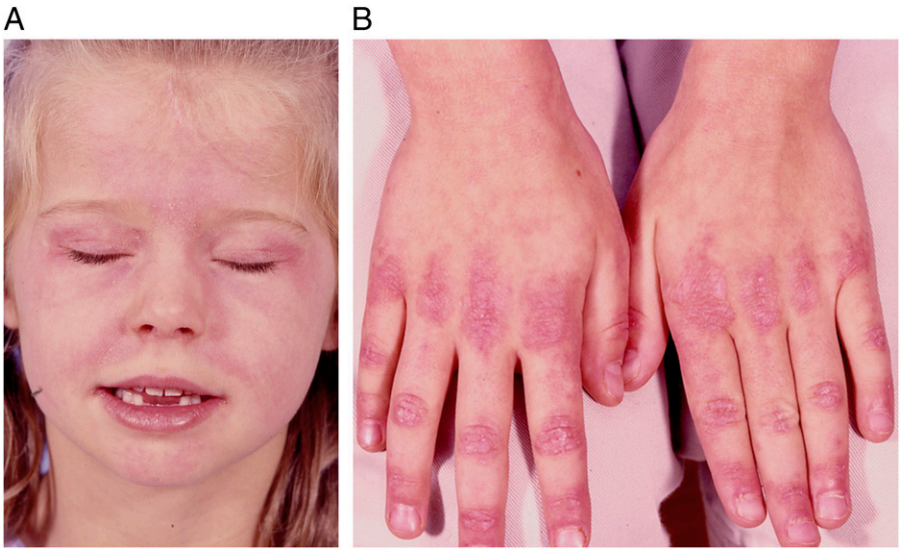

Figure 4. A. Dermatomyositis facial rash, with erythematous confluent scaly plaques over the forehead, upper eyelids, and cheeks. B. Dermatomyositis hand rash, with erythematous scaly plaques predominantly overlying the extensor surface of joints, associated with flat-topped shiny Gottron papules.

to transfer or ambulate safely, inability to swallow secretions or coughing that suggests aspiration, respiratory weakness that suggests a need for ventilatory support, or appendicitis-like abdominal pain that suggests intestinal perforation.

For the patient described in the case presentation, DM could explain every one of the features of her problem list, not just RP and facial rash.

Diagnostic Approach

The 1975 diagnostic criteria of Bohan and Peter (8) are still the primary diagnostic criteria in use. These criteria include characteristic skin changes and elevated skeletal muscle enzymes, as well as evidence on manual muscle testing of proximal muscle weakness, evidence of myopathy by electromyography, and evidence of characteristic muscle cell injury and inflammation on muscle biopsy.

The muscle enzymes that can become elevated from muscle cell injury include creatine kinase, aspartate aminotransferase, lactate dehydrogenase, and aldolase. The pattern of elevation can vary over time, and the creatine kinase level (which is muscle specific) may not always be informative. Because the other enzymes have multiple sources, other tests (such as other liver function tests or a complete blood cell count) may need to be performed at the same time to aid interpretation.

Magnetic resonance imaging (MRI) of the proximal musculature, usually the thighs and pelvis, can also identify muscle injury and help guide site selection for a diagnostic muscle biopsy. An MRI and muscle biopsy may not seem needed when the diagnosis is obvious, but they can sometimes provide important diagnostic and prognostic information regarding the extent and severity of the inflammatory process and tissue damage and thereby impact decisions about initial therapy. Electromyography is performed much less commonly now since the introduction of MRI for evaluating DM.

Other common laboratory tests, such as basic hematology and chemistry panels, markers of inflammation, and markers of immune activation, are often normal or nonspecifically abnormal. Myositis antibodies, mentioned earlier, are abnormal in a minority of patients and are not yet universally obtained. Production of ANA is not a feature of DM.

Management

As with other complex multisystem diseases, it is important to characterize the extent of involvement to plan optimal therapy. A key step in the early evaluation and management is to assess the patient's functional limitations and safety in their home or school environment. Physical and occupational therapy evaluations can help in this regard, and there are standardized evaluation tools available to assist with tracking improvement over time. When there are severe manifestations, urgent multidisciplinary evaluation may be needed, including assessment of airway safety and pulmonary sufficiency, and intense medical therapy may need to be initiated before all results are available.

More commonly, medical therapy is started after the medical evaluation is complete. Glucocorticoids provide quick anti-inflammatory and immunosuppressive benefits but are almost always paired with additional anti-inflammatory and immunomodulatory therapies that help reduce glucocorticoid dependence and toxicity. The most commonly added anti-inflammatory medication is weekly low-dose methotrexate, given orally or subcutaneously. Similar to SLE, a variety of other corticosteroid-sparing medications can be used, including hydroxychloroquine, and potent immunosuppressives, such as calcineurin inhibitors (cyclosporine or tacrolimus), azathioprine, and mycophenolate mofetil. In urgent situations, intravenous immunoglobulin 2 g/kg is often used to gain quick control of the disease and can be repeated every 2 to 4 weeks. As with severe vascular diseases, there is sometimes a need for even more intensive therapies, including cyclophosphamide or rituximab.

Prognosis and Follow-up

Traditionally, children with DM are noted to follow 1 of 3 equally common patterns, including a group having a monophasic course with little or no residual effects, a second group having a relapsing course with highly variable results, and a third group with severe and chronic ulcerative disease. New insights learned from profiling based on myositis antibody and more detailed muscle pathology studies may allow for better subclassification of patients and tailoring of therapies for optimal care. The principles mentioned previously herein for SLE regarding setting expectations and encouraging teamwork and support are just as true for DM because most do not have a monophasic course, and DM's effect on all groups is significant.

SCLERODERMA

Definition

Scleroderma includes several inflammatory conditions that result in hardening of the skin due to fibrosis. They are commonly divided into 2 general categories. Those conditions known as a form of localized cutaneous scleroderma primarily involve the skin and sometimes adjacent deeper tissues. The conditions known as a form of systemic scleroderma (systemic sclerosis) may have a variety of additional

manifestations, including life-threatening involvement of internal organs. Fortunately, most children with scleroderma have a form of localized cutaneous scleroderma rather than a systemic form.

Epidemiology

Scleroderma is estimated to affect approximately 300,000 individuals in the United States, most commonly affecting adults and more commonly affecting females.

Pathogenesis and Presentation

Although the etiology of scleroderma is unknown, as with other autoimmune disorders there is a role for genetic predisposition. Its pathogenesis features endothelial injury leading to loss of vascular integrity and subsequent edema, inflammation, and ultimately fibrosis. Vascular injury can also lead more directly to tissue damage, including necrosis of skin and other tissues. With systemic forms, the integrity and function of internal organs can be compromised and may result in life-threatening cardiopulmonary, renal, and visceral disease.

Symptoms and Signs

During the inflammatory phase there may be erythema or violaceous discoloration of skin, along with edema and pain. As with other conditions causing skin injury, there can be a postinflammatory hyperpigmentation or hypopigmentation, but often there are other notable findings that distinguish it from more common causes of skin injury, such as sun damage, trauma, or infection. In many cases, the fibrosis will manifest with discrete plastic-like firmness of the skin or subcutaneous tissue, and in some there will be a smooth, waxy hypertrophic appearance (Fig 5A). In other cases, there will be tissue injury, leading to localized atrophy of the skin and subcutaneous tissues, leaving the skin almost translucent and underlying structures (tendons, muscles) more easily discerned. The soft tissue injury may progress to involve deeper layers, leading the skin to become adherent to deeper tissues and even restricting the normal growth and development of cutaneous and musculoskeletal structures (Fig 5B). Restriction of the normal motion of joints may result. Many patients will have individual lesions of more than 1 type or lesions with mixed features, including a mixture of hyperpigmentation and hypopigmentation, atrophy, and hypertrophic fibrosis in linear and irregular plaque shapes.

For the patient described in the case presentation, systemic scleroderma would explain many features of her problem list, including RP, but not the scaly nature of her skin involvement.

Diagnostic Approach

Diagnosis of the skin disease is often made on clinical grounds but may also be confirmed by biopsy. There are no diagnostic laboratory tests for localized scleroderma. There can be evidence of immune activation with an elevated serum IgG or a nonspecifically positive ANA test, as well as nonspecific elevation of inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein. The distinction of localized forms from systemic forms is generally based on a thorough history and physical examination. Symptoms and signs that would suggest systemic disease include RP, ulcers of the digital tips, or other vascular events, as well as tenosynovitis, joint synovitis (arthritis), myositis, fasciitis, dysphagia or gastroesophageal reflux, or cardiorespiratory symptoms. As with SLE, a quick review of the consensus criteria can quickly facilitate recognition of important clues in the history or physical

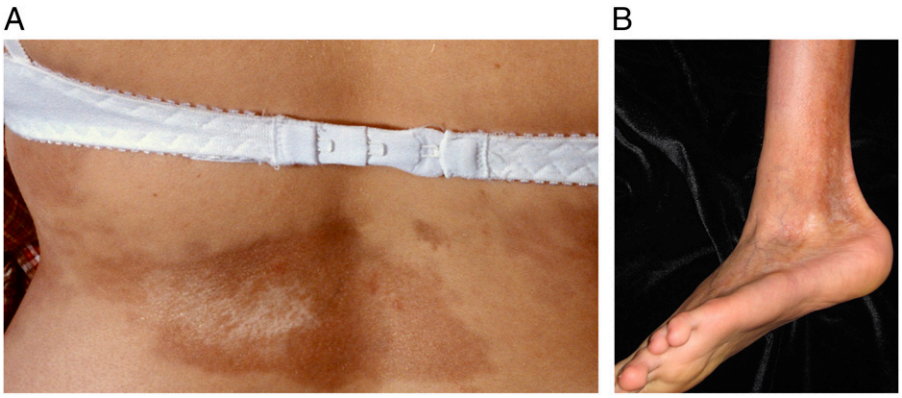

Figure 5. A. Localized cutaneous scleroderma (plaque morphea) on the back, with postinflammatory hyperpigmentation and hypopigmentation, waxy sclerosis, and atrophy. B. Localized cutaneous scleroderma (linear scleroderma) extending down the left lower leg, over the lateral malleolus, onto the dorsum of the foot, with marked postinflammatory hyperpigmentation and hypopigmentation, waxy sclerosis, and atrophy of subcutaneous tissues, resulting in vascular prominence.

examination that might facilitate assessment of whether a systemic illness seems likely (Table 3). In cases in which there may be extensive involvement of the skin or symptoms raising the question for systemic disease, testing for autoantibodies may be informative. With systemic forms of scleroderma, the ANA screen is often positive, with anticentromere or anti–scleroderma 70 specificities.

Management

Both local and systemic therapies are used for localized scleroderma. For limited disease that does not have significant cosmetic or functional implications, local therapy with immunomodulatory medications can be used, including topical or intralesional glucocorticoids, topical vitamin D analogues, or topical calcineurin inhibitors such as tacrolimus. For lesions causing significant cosmetic or functional implications, such as facial lesions or lesions affecting limb growth or function, systemic therapy is essential and rehabilitative services may be needed.

Options for systemic therapy continue to evolve and have significantly changed the management of localized cutaneous scleroderma during the past 25 years. Low-dose oral or subcutaneous methotrexate, as used for juvenile arthritis and DM, can help arrest progression and even allow remodeling and healing of lesions. Mycophenolate mofetil and other immunosuppressive therapies can be helpful for resistant disease, and there has been success reported with newer biological therapies currently approved for juvenile arthritis. For highly inflamed, symptomatic, or rapidly progressive disease, the addition of oral or intravenous glucocorticoids can help quickly reduce inflammation and provide time for methotrexate or other therapies to begin to work. The best methods for assessing residual active disease and, therefore, the timing of therapy withdrawal are still unknown and are an area of active research.

TABLE 3. PRES/ACR/EULAR Classification Criteria for Juvenile Systemic Sclerosis

A patient may be classified as having juvenile systemic sclerosis in the presence of the major criterion and 2 minor criteria.
Major criterion: Proximal skin sclerosis or induration
Minor criteria:
• Skin: sclerodactyly
• Vascular: Raynaud phenomenon, abnormal nail fold capillaries, digital tip ulcers
• Musculoskeletal: tendon rubs, arthritis, myositis
• Gastrointestinal: dysphagia, gastroesophageal reflux
• Pulmonary: pulmonary fibrosis, low diffusing capacity, pulmonary hypertension
• Cardiac: arrhythmias, failure
• Renal: renal crisis, new hypertension
• Neurologic: neuropathy, carpal tunnel
• Serologic: ANA or SSc-selective antibodies (anticentromere, Scl-70, and others)

ACR=American College of Rheumatology, ANA=antinuclear antibody, EULAR=European League against Rheumatism, PRES=Pediatric Rheumatology European Society.
Adapted with permission from Zulian F, Woo P, Athreya BH, et al. The Pediatric Rheumatology European Society/American College of Rheumatology/European League against Rheumatism provisional classification criteria for juvenile systemic sclerosis. Arthritis Rheum. *2007;57(2):203–212. (9)*

TABLE 4. Distinctive Features of the Major Multisystem CVDs/CTDs

CONDITION	DISCERNING FEATURES
SLE	• Extensive multisystem (head-to-toe) involvement possible. Cytopenias, renal, and erythematous skin disease in most • ANA screen nearly always positive, and anti-dsDNA and anti-Smith are unique. Decreased C3 and C4 common
DM	• Erythematous scaly rash of face and joints, and proximal muscle weakness and elevated muscle enzymes • ANA screen negative
Scl	• Smooth, hardened skin with hyperpigmentation and hypopigmentation. Multisystem form is rare, with the rash unlike other SLE and DM • ANA screen often positive, and anti–Scl-70 or anticentromere specificities are unique
MCTD	• "Mixed" features of SLE, DM, Scl, and RA, but not renal disease • ANA screen nearly always positive, and anti-ribonucleoprotein antibody specificity always present and predominant

ANA=antinuclear antibody, CVD/CTD=collagen vascular disease/connective tissue disease, DM=dermatomyositis, dsDNA=double-stranded DNA, MCTD=mixed connective tissue disease, RA=rheumatoid arthritis, Scl= scleroderma, SLE=systemic lupus erythematosus.

Prognosis and Follow-up

At minimum, the hope is to arrest any progression of the disease, but often there will be fading and softening of fibrotic lesions and even reconstitution of subcutaneous tissue in atrophic areas. With optimal therapy there is the potential for normal growth and reconstitution of the soft tissue and deeper structures. Surgery to improve soft tissue or skeletal abnormalities is best performed only when the patient is in remission of medications because healing may otherwise be compromised.

CASE EXAMPLE PART 2: DIAGNOSTIC CONSIDERATION AND TESTING

Given the patient's rapidly growing problem list, the pediatrician screened for infectious, endocrine, oncologic, and rheumatic diseases that might explain her many problems. Testing for Epstein-Barr virus infection was negative. Electrolyte concentrations, creatinine level, and urinalysis results were normal, excluding any significant renal disease. Her thyrotropin level was normal. Blood counts were reassuring, with a white blood cell count of 4,200/μL (4.2×10^9/L), hemoglobin level of 12.8 g/dL (128 g/L), and platelet count of $286\times10^3/\mu$L (286×10^9/L). The uric acid level was low normal, and the lactate dehydrogenase level was only borderline elevated, suggestive of an inflammatory process rather than a malignancy. The C-reactive protein level was normal, but the erythrocyte sedimentation rate was elevated at 58 mm/h (reference range, ≤20 mm/h), consistent with active inflammation. The RF was strongly positive and the ANA screen was strongly positive.

Additional follow-up laboratory tests within a week showed elevation of the creatine kinase and aldolase levels and a hepatic panel with a borderline elevated aspartate aminotransferase level. There was mild lymphopenia (absolute lymphocyte count, 900/μL [0.9×10^9/L]). Specific ANA testing was negative for anti-dsDNA, but the anti–extractable nuclear antigen (anti-ENA) antibody panel was positive for anti-ribonucleoprotein antibody (anti-RNP) and negative for Smith antibody, Sjögren antibodies, and scleroderma antibodies.

AN APPROACH TO "RHEUMATOLOGY TESTS"

It is common practice for physicians to order "rheumatology tests" to screen for rheumatic diseases, but in children this is not an effective strategy. The best strategy is to establish a list of the most likely diagnoses and then use tests to increase or decrease the probability of alternative diagnoses and clarify the prognosis (Table 4).

In the case of the RF test, it is not specific to RA or to the childhood equivalent (RF-positive polyarticular JIA), which is a relatively infrequent arthritis in children. The RF test is often nonspecifically positive with infectious illnesses, including common infections as well as less common infections that can be associated with persistent problems, such as subacute bacterial endocarditis. It can also be positive in rheumatic diseases other than RA, such as SLE and MCTD.

Similarly, the ANA test is not specific and most commonly is not an indication of a health problem. In children, the background rate of positive results is approximately 25%, most often triggered by minor infectious illnesses. It is a commonly positive result in many subtypes of JIA, but its utility is not for diagnosis but rather for identifying the risk of developing a uveitis and establishing the frequency of screening ophthalmologic examinations. As mentioned, it is virtually always positive in SLE, and although it is an important confirmatory test for SLE, a negative result is what is often most informative because it makes this diagnosis highly unlikely. When there is a positive result, and SLE or a similar condition associated with specific ANA is suspected, then testing for specific ANAs can help clarify a diagnosis. The target antigens in the nucleus include native (double-stranded) DNA, or RNA-protein complexes. The physician can order a specific screening test for anti-dsDNA antibody and then screen for the other targets using an anti-ENA antibody panel. Antibodies against dsDNA are specific for lupus, as is the Smith antibody specificity in the anti-ENA antibody panel. Because these tests detect only a subset of specific ANAs, there is no reason to order these when the screening ANA result is negative.

Antibodies specific to scleroderma are commonly included in the anti-ENA antibody panel and are associated with systemic scleroderma. Antibodies associated with Sjögren syndrome are also part of the ENA panel but are not entirely specific to Sjögren and can be seen in SLE and other more limited forms of lupus, including neonatal lupus. Finally, anti-RNP antibody is a part of the ENA panel and occurs at lower values in SLE, but when it is present at high values and is the only positive specific antibody, anti-RNP suggests the diagnosis of MCTD, an interesting overlap condition that can have features of RA (including RF), SLE (but usually not renal disease), DM, and scleroderma. Mixed connective tissue disease should be considered in the list of possible diagnoses whenever a patient has RP or symptoms and signs suggestive of SLE, DM, RA, or scleroderma. Suspicion of MCTD should prompt ordering of a screening ANA and, if positive, then specific ANA testing.

CASE EXAMPLE PART 3: INTERPRETATION AND DIAGNOSIS

This patient had a symmetrical polyarthritis, which raised the possibility of RA. However, she had many extra-articular symptoms and signs, which suggested something more complex than RA. The patient also had muscle injury with elevated muscle enzyme levels and contractures, and the CVDs/CTDs that come to mind are DM, followed by SLE, and possibly scleroderma. The patient's rash was scaly, rather than smooth or fibrotic, so scleroderma was not a likely explanation. In contrast, a scaly malar rash is seen with both DM and SLE, and a scaly rash on joints of the hands is particularly suggestive of DM. When present, renal disease with active urinary sediment is suggestive of SLE, but this patient had no such difficulties. Otherwise, SLE is one of the few CVDs/CTDs that is multisystem and associated with RF and multiple other autoantibodies. Given that the patient had overlapping features of RA, DM, and SLE, it is not surprising that she turned out to actually have the overlap condition MCTD, as confirmed by a positive ANA test result that was uniquely associated with only the anti-RNP antibody specificity.

MANAGEMENT OF CVDs/CTDs

The CVDs/CTDs may cause both immediate and long-term problems, and the chance for and occurrence of such problems should not be underestimated but rather addressed head-on. The goals should be, in theory, to achieve disease remission and promote normal growth and development and a full and active life. More realistically, the goals are to make the patient healthier, minimizing any potential negative effects of therapy, and (as much as possible) to keep the child's condition and its treatment from interfering with a full and active life.

Many people are concerned about the therapies used for rheumatic diseases. It is important to emphasize that they are generally safe and effective when prescribed and monitored appropriately and that our knowledge about how to best help children with rheumatic diseases is improving all the time. Collaborative research networks are performing important work that continues to refine our understanding of the natural history of these conditions, the therapies, and how to optimize patient-centered care.

As for any child, but even more so for a child with a serious illness, a good working relationship with a primary care provider (and the clinic staff) for well-child care and acute illnesses is important. Prevention of infections through appropriate immunizations, and easy access for evaluation and management of new infectious illnesses, is especially important for these children given that these conditions and their treatment affect the child's ability to fight infections.

However, the primary care provider also plays an important role in making sure that the child's other general health needs are not negatively affected by his or her rheumatic disease and its treatment. They may have a better picture of the whole child and the family and the community in which they live through regular follow-up well-child care and may better know when and where special attention is needed. For example, the negative effects of glucocorticoid therapy include direct effects on the child (eg, visible effects on appearance, growth, or behavior, and less visible effects on bone, ocular, and cardiovascular health) and on the child's interactions with friends and family. Support from their families, medical professionals, and community organizations can have a hugely positive impact for patients newly diagnosed as having a chronic health condition and can promote their successful transition back to wellness.

Summary

- The conditions known as collagen vascular diseases (CVDs) or connective tissue diseases (CTDs) are individually uncommon, and their myriad symptoms and signs may appear asynchronously and highly variably.
- Timely and accurate recognition of the more common CVDs/CTDs can be facilitated through the familiar steps of collecting a comprehensive medical history, performing a complete physical examination, and creating a detailed list of past and current problems.
- The problem list for a child with a CVD/CTD may at first suggest a broad list of diagnostic possibilities. To sort out the possibility of a CVD/CTD, the published classification criteria can provide a quick reminder of their most distinctive features and help suggest appropriate next steps for further evaluation.
- Research evidence (1) and consensus suggest that if laboratory or imaging studies are needed for the evaluation of CVDs/CTDs, it is best to start with common tests that are easily obtained and quickly reported rather than with extensive and expensive "rheumatology tests."
- For concerning cases, such as children with rapidly growing multisystem problem lists, early discussion with a pediatric rheumatologist can help patients, parents, and providers feel assured that the plans for evaluation, treatment, and possible referral are on the mark.

References for this article are at http://pedsinreview.aappublications.org/content/39/10/501.

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1. You are evaluating a 12-year-old boy in your practice who has a history of several weeks of on-and-off fatigue and joint pain. The patient also has recent weight loss. He has had 2 episodes of nonstreptococcal pharyngitis. You suspect that he may have systemic lupus erythematosus (SLE), and you are considering ordering an antinuclear antibody (ANA) test. Which of the following is the most accurate characteristic of the ANA test and its role in establishing the diagnosis of SLE?

   A. A negative ANA test result helps rule out SLE.
   B. A positive ANA test result needs no follow-up testing.
   C. Has a high positive predictive value.
   D. Is highly specific.
   E. Is positive in approximately 50% of the healthy population.

2. A 15-year-old adolescent girl, who is followed up in your clinic, has recently been diagnosed as having SLE with mild renal involvement based on clinical criteria and a positive ANA test result. She has no mucocutaneous features. Her complete blood cell count is normal except for mild anemia. In addition to nonsteroidal anti-inflammatory drugs for managing the fevers and arthritis, which of the following is the most appropriate initial treatment regimen in this patient?

   A. Glucocorticoids.
   B. Hydroxychloroquine.
   C. Intravenous immunoglobulin.
   D. Plasmapheresis.
   E. Rituximab.

3. An 8-year-old boy is brought to the clinic with a 2-day history of heliotrope discoloration of the upper eyelids. In addition, the patient was noted 1 to 2 days earlier to have a symmetrical papular rash over the extensor surfaces of the joints, particularly the proximal interphalangeal, metacarpophalangeal, distal interphalangeal, elbow, and knee, consistent with Gottron papules associated with shiny, erythematous, scaly plaques. The patient has had multiple visits to the emergency department in the past 2 to 3 months for fevers, malaise, fatigue, and weight loss. Evaluations for infections and malignancy have been negative. Today, the parents noticed the discoloration of the upper eyelids and the rash and brought the child to the clinic for further investigation and management. You suspect one of the juvenile idiopathic inflammatory myopathies, particularly juvenile dermatomyositis. Which of the following clinical and/or laboratory findings is part of the Bohan and Peter criteria for the diagnosis of juvenile dermatomyositis in this patient?

   A. Anemia of chronic disease.
   B. Distal muscle weakness.
   C. Elevated serum levels of skeletal muscle enzymes.
   D. Family history of dermatomyositis in a first-degree relative.
   E. Migratory muscle weakness.

4. The patient in the previous question underwent a full evaluation. Serum levels of skeletal muscle enzymes, including creatine kinase, aspartate aminotransferase, lactate dehydrogenase, and aldolase, were elevated. Physical examination was significant for weakness in his upper and lower extremities and difficulty combing his hair. Electromyographic and magnetic resonance imaging findings were consistent with juvenile dermatomyositis. Which of the following is the most appropriate next step in initial management in this patient?

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A. Cyclophosphamide.
B. Intravenous immunoglobulin.
C. Nonsteroidal anti-inflammatory drugs.
D. Prednisone.
E. Tacrolimus.

5. A 16-year-old girl developed multiple large areas of waxy hyperpigmentation and hypopigmentation on her legs and back. These skin changes have been progressing over the past 12 to 18 months. Periungal capillary changes are noted along with a progressively worsening perfusion and bluish discoloration of her fingers. Scleroderma is suspected. In addition to the findings described above, which of the following clinical findings is expected to be seen in the systemic form of this disease in this patient?

A. Dysphagia.
B. Generalized lymphadenopathy.
C. Headaches.
D. Hepatosplenomegaly.
E. Visual changes.

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