A 17-year-old female presented with a 6-week history of fatigue and a 2-week history of mild swelling of her hands and ankles. She complained of diffuse joint pain, intermittent nausea, dyspnea on exertion, and headache. She also reported that her fingers "changed colors in the cold." During the previous month, she had taken acetaminophen almost daily for low-grade, intermittent fevers. In the previous 4 days, she had developed a rash on her inner thighs and arm, with recurrent nausea, generalized myalgias, intermittent back pain, heat and cold intolerance, and weakness.

Her past medical history was significant for recurrent urinary tract infections in early childhood, and a cholecystectomy and tonsillectomy in the previous 2 years. Menarche had begun at age 10 years. She experienced "irregular" menstrual cycles, and her last menses was 18 months before presentation. Her only medication was intramuscular medroxyprogesterone acetate every 3 months. She denied being sexually active.

Family history was significant for diabetes mellitus, cardiovascular disease, rheumatoid arthritis, osteoarthritis, hyperlipidemia, thyroid disorders, and various cancers, including childhood leukemia.

On physical examination, the afebrile patient appeared well. Her body mass index was 29, and her heart rate was 120.

Abnormal findings included nonpitting bilateral lower leg edema and a papular erythematous rash ...

Her bilateral hand grip was weak, and upper extremity strength was rated as 4/5 on the left and 5/5 on the right. The rest of her neurological assessment was normal.
Laboratory studies included a normal urinalysis, complete blood count, serum electrolytes and blood urea nitrogen, and creatinine, as well as a negative pregnancy test. Her lactate dehydrogenase (LDH) was 669 U/L; antistreptolysin-O titer was 45 IU/mL, and her C-reactive protein (CRP) was 3.276 mg/dL. A thoracic echocardiogram was normal. Further study results included a normal chest radiograph, and a right upper quadrant ultrasound with an incidental finding of a duplex collecting system on the right, and a renal ultrasound that confirmed this incidental finding.

Because of the continuation of the patient’s symptoms while hospitalized, on approximately day 3, more laboratory studies were obtained: a sedimentation rate of 20 mL/min, and repeat blood counts and electrolytes, which were unremarkable. Other unremarkable studies included her complement 3 and 4, alkaline phosphatase, and gamma-glutamyl transpeptidase levels. The aspartate aminotransferase, alanine aminotransferase, and LDH levels were mildly elevated, while the creatine kinase (CK) level was markedly elevated at 12,630. A repeat CRP was 10.62 mg/dL. P-ANCA and C-ANCA, anti-Smith antibody, anti-mitochondrial antibody, anti-SS-A antibody, and anti-SS-B antibody screens were all negative. However, her ANA value was 1:320 in a speckled pattern, and her anti-ribosomal protein antibody (anti-RNP) was positive at 86 AU/mL. Muscle biopsy revealed inflammatory myopathy, a relative type 2 myofiber atrophy.
Prednisone was initiated at 40 mg in the morning and 20 mg at night. The patient improved clinically within 1 day, along with decreases in her CK and AST levels. She was discharged from the hospital within the next week, with resolution or improvement of all of her symptoms.

Discussion

There is limited information on the epidemiology of MCTD in the US. In a retrospective study of 12 female children in Taiwan, it was found that the mean age of onset was 10.7 years. Oetgen and colleagues reported that the onset of MCTD was between the ages of 11 and 18 years. As more diagnoses of MCTD are made, perhaps larger studies can be done specifically on the investigation of MCTD in the pediatric population.

MCTD can present with many combinations of symptoms because, by definition, it is an overlap syndrome. There have been two other sets of criteria established: the Kasukawa and Porter criteria. The Kasukawa criteria require the presence of a positive anti-RNP antibody and certain common symptoms and disease findings resembling other rheumatological conditions, including lupus, polymyositis, and systemic sclerosis. The production of anti-RNP antibodies that activate inflammation pathways is theorized to be the underlying mechanism of MCTD symptomatology. A review by Hoffman and Maldonado describes some studies that report associations with HLA-DR4 and parts of chromosome 3 with MCTD. The presence of anti-U1 RNP antibodies is strongly suggestive of MCTD and is included in all three sets of criteria. These anti-ribosomal antibodies are thought to be the cause of the disease and clinical manifestations. Patients typically have a high titer of anti-RNP antibodies. The cellular role of anti-RNP antibodies includes increasing cytokine action; the full role in the production of manifestations of the disease still needs to be elucidated.

The diagnosis can be challenging because of the varied appearance of symptoms over time. For example, as time progresses, patients may also eventually develop pericarditis, dry eyes and mouth, psychosis, and hematologic abnormalities (thrombocytopenia or anemia). Including MCTD in the differential diagnosis of a child’s multi-system illness is the first step to diagnosing MCTD properly.

In this case, once the disease was considered, the diagnosis was established promptly. The greatest clues for MCTD were provided by the history of questionable Raynaud’s phenomenon and diffuse muscle tenderness, the physical examination findings of the rash, and abnormal laboratory studies of an elevated serum CK level. The constellation of findings prompted a rheumatologic consultation that guided the subsequent evaluation and treatment.

A rheumatology consultation is imperative for treatment guidance. Therapy usually involves oral corticosteroids, but will be established on a case-by-case basis depending on the specific manifestations of the disease. The primary care pediatrician will manage the overall health care needs of the child with this chronic illness, including
facilitating referrals for ancillary services such as physical therapy.

CONCLUSION

The child with MCTD will first present to the pediatrician with myriad distressing symptoms. Although uncommon, MCTD should be on the list of suspected disorders, especially when there is a history of Raynaud’s phenomenon, diffuse muscle tenderness, rash, and an elevated serum CK level.

REFERENCES