

Revisiting Idiopathic Inflammatory Myopathies

By Lucy Lu Chu, MD; and Ophir Vinik, MD, FRCPC, MScCH

Patient Case:

A 27-year-old woman, who used to be physically active, was referred to a rheumatologist by her family doctor for joint pain. She described six months of stiffness in the upper arms and thighs with progressive decrease in proximal muscle stamina and exercise tolerance. She was previously healthy with no medication, alcohol nor recreational drug use. Family history was negative for autoimmune or muscle disorders. On examination, she had mild weakness in the deltoids, biceps, and hip flexors rated as 4+/5 on the Medical Research Council (MRC) scale. There were no swollen joints. Dermatologic examination was negative for rashes, but mild nail-fold capillary dilatations were present. Initial bloodwork was normal including C-reactive protein of 0.7 (N < 5) and creatine kinase (CK) of 81 (N 20-210). Anti-nuclear antibodies (ANA), rheumatoid factor (RF), and anti-cyclic citrullinated peptide (anti-CCP) were negative. The only identified abnormalities were an erythrocyte sedimentation rate of 37 (N < 30), and lactate dehydrogenase of 292 (N 140-225).

Due to findings of proximal muscle weakness and abnormal nail-fold capillaries, additional tests were performed. Myositis-specific antibody (MSA) panel returned positive for anti-nuclear matrix protein 2 antibody (NXP2). Magnetic resonance imaging (MRI) demonstrated extensive patchy muscle edema involving the gluteal, iliopsoas and quadriceps musculature bilaterally. Subsequent quadriceps muscle biopsy revealed a distinct pattern of perifascicular atrophy, accompanied by perivascular and septal lymphohistiocytic inflammatory cell infiltrate, with numerous tubuloreticular inclusions. This confirmed a clinical-serological-pathological diagnosis of dermatomyositis.

Introduction

Idiopathic inflammatory myopathies (IIM) encompass a heterogeneous group of rare, autoimmune conditions characterized by various degrees of proximal muscle, cutaneous, and sometimes multi-organ involvement. There is growing recognition that IIM is not a single entity but rather a spectrum of clinical-serological-pathological entities.¹ Severity of the different manifestations, even within an entity, can vary widely. Incidence of IIM is estimated at 1 per 100,000 and can occur throughout the life span with overall female predilection.²

Clinical Features

Classical dermatomyositis is characterized by proximal muscle weakness and prototypical skin rashes, including Gottron's papules and poikilodermic changes, such as the heliotrope, shawl, V-neck and Holster signs. Diagnosis can become challenging in patients lacking overt muscle weakness or characteristic rashes.³ Normal CK does not rule out active myositis, as about 15% of patients with active dermatomyositis can have normal CK.⁴ Typical histological findings of classical dermatomyositis include perifascicular atrophy with inflammatory infiltrate and tubuloreticular inclusions on electron microscopy.³ Dermatomyositis may also present as part of an overlap syndrome with features of other connective tissue diseases, such as systemic sclerosis.

Another clinical entity within the IIM spectrum is anti-synthetase syndrome. It is a heterogeneous entity that may involve inflammatory arthritis, mechanic's hands, Raynaud's phenomenon, and interstitial lung disease. It is associated with the presence of antibodies directed against transfer ribonucleic acid (tRNA) synthetase enzymes.³

Immune-mediated necrotizing myositis (also known as necrotizing autoimmune myopathy, NAM) is generally characterized by severe weakness with markedly elevated CK levels but typically no skin rashes. While NAM can be idiopathic, some cases are induced by medication exposure, particularly statins. HMG-CoA reductase antibodies might be identified to help support the diagnosis. Muscle biopsy findings include macrophage-mediated necrotic muscle fibers with minimal or absent inflammatory infiltrate.⁵

Inclusion Body Myositis (IBM), previously included as one of the IIM, is a different disease entity, being a degenerative condition involving both proximal and distal muscles

and characterized by lack of response to immunosuppression. Histopathology shows rimmed vacuoles with inclusion bodies.⁶ Polymyositis is vanishing as a discrete diagnostic entity. Traditionally, it was characterized by lack of typical skin rashes and histological findings of perimysial involvement.⁷ Better clinical-serological-pathological evaluation would now commonly reclassify the disease as either IBM, necrotizing myopathy or antisynthetase syndrome.⁸

Diagnosis

Detailed clinical history and physical exam are crucial in assessment of patients with possible IIM. MSA are identified in up to 80% of IIM patients.⁹ A negative ANA, seen in 40-60% of dermatomyositis patients, does not rule out the disease nor the possibility that MSA are present.¹⁰

Electromyography (EMG) can be helpful in identifying an underlying myopathic or neuropathic process. Used on its own, however, it cannot establish a diagnosis of IIM.¹¹ Muscle MRI is an increasingly employed diagnostic tool. T2 weighted images with fat suppression or short tau inversion recovery (STIR) sequencing can identify muscle edema.¹¹ While muscle edema is not specific to IIM, the presence of proximal and symmetric involvement in the appropriate clinical context can be helpful. MRI can also detect areas of atrophy and fat replacement, thus differentiating active from chronic changes of myositis. This can guide site selection for biopsy to reduce the rate of false-negative results, which may be as high as 45% in blind muscle biopsies for DM.¹¹ Proper sample processing is vital and pathological assessment should include electron microscopy to identify certain pathologic features such as tubuloreticular inclusions.¹²

The commonly used Bohan and Peter diagnostic criteria from 1975¹³ are fraught with limitations. They do not capture many of the advances in the field such as the diagnosis of IBM or availability of MSA.¹⁴ The more recent 2017 EULAR/ACR criteria, while providing a better framework with sensitivity and specificity of up to 93% and 88% respectively when muscle biopsy is included,¹⁵ still do not adequately encapsulate the broad heterogeneity of these conditions. These criteria also do not incorporate MSA and still consider polymyositis as a distinct entity. Ongoing efforts to further improve classification and diagnostic tools for clinicians are needed.¹⁶

Management

IIM are treatable conditions requiring a combination of non-pharmacological and pharmacological interventions. The choice of treatment should be tailored based on clinical manifestations and severity. A multidisciplinary approach is recommended to manage the various systemic aspects. Physiotherapy, occupational therapy and rehabilitation services have well-established benefits.^{18,19} Speech language therapists can assess the need for diet modifica-

tion if there is dysphagia from striated muscle involvement in the upper one-third of the esophagus.

High-dose prednisone is the mainstay of initial pharmacotherapy. Typical starting dose is 1-1.5 mg/kg/day.²⁰ Steroid-sparing options include methotrexate, mycophenolate mofetil and azathioprine. Intravenous immunoglobulin is an adjunct treatment in patients presenting with more severe muscle and cutaneous disease.²¹ Of note, the extent of CK elevation may not correspond to the clinical degree of muscle weakness, and normalization of CK with treatment does not necessarily define disease remission. In some patients, CK fluctuates or never fully normalizes despite clinical remission.

In adult-onset IIM, malignancy risk within the first five years of diagnosis is up to six-fold the average population, particularly with classical dermatomyositis.²² No evidence-based guidelines exist for malignancy screening in IIM patients. Features found to have strong malignancy association in dermatomyositis include male gender; onset of disease after the age of 50; classical skin rashes; rapidly progressive disease; clinical features concerning for malignancy; and positive anti-nuclear matrix protein 2 (NXP2) or transcription intermediary factor 1-gamma (TIF1- γ) antibodies.²³ Computed tomography of chest/abdomen/pelvis, esophagogastroduodenoscopy, and colonoscopy should be considered in these patients.²³ The positron emission tomography (PET) scan has been shown to be equivalent to these screening modalities.²⁴ Treatment of malignancy, while essential, is commonly insufficient to treat the associated dermatomyositis manifestations. Concurrent immunosuppression is required in close collaboration with the treating oncology team. In cancer-associated dermatomyositis patients who are in remission, recurrence of cutaneous or muscle manifestations may signify cancer recurrence.²⁵

Back to the Case:

The patient was started on high-dose prednisone and azathioprine alongside an exercise program for proximal muscle strengthening. She responded well to treatment with complete resolution of weakness and nail-fold capillary abnormalities. The patient tapered off prednisone with no recurrence of symptoms and remains on maintenance treatment with azathioprine.

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