

Updates in Diagnosis and Management of Polymyositis

Abstract

Polymyositis (PM) is an autoimmune disorder, result from abnormal activation of cytotoxic T lymphocytes (CD8 cells) and macrophages against muscular antigens as well as the strong extrafusal muscular expression of major histocompatibility complex class 1 causing damage to the endomysium of the skeletal muscles. Polymyositis develops over the months as compared to inclusion body myositis (IBM), which is a slowly progressive chronic myopathy developing in older individuals over a period of months to years with more severe symptoms. The principal goals of therapy are to improve strength and improve physical functioning. Many patients require treatment for many years. Polymyositis affects the distal musculature of the esophagus in the late stage of disease in up to 70% of the patients leading to the inability to swallow, as well as regurgitation problems that can cause aspiration pneumonia. The principal goals of therapy are to improve strength and improve physical functioning. Many patients require treatment for several years. The 5-year survival rate for treated patients is in the order of 95%. Up to one-third of PM patients may be left with some degree of residual muscle weakness.

Keywords: Polymyositis, inclusion body myositis, pneumonia, strong extrafusal muscular expression

Introduction:

Polymyositis is considered one of idiopathic inflammatory myopathies which involve four major subtypes: polymyositis, dermatomyositis, inclusion body myositis, and necrotizing myopathy. (1) Polymyositis, an autoimmune and chronic inflammatory myopathy, is characterized by symmetrical proximal muscle weakness due to the presence of inflammatory infiltrates in striated muscles. There is involvement of endomysial layers of skeletal muscles unlike dermatomyositis, which involves the perimysial layers of muscles along with dermatological presentations. (2) PM may also occur as part of the spectrum of other rheumatic diseases like systemic lupus erythematosus (SLE) and mixed connective tissue disease. Moreover, inflammatory

myopathy may result from some drugs as (procainamide, D-penicillamine), and viruses, most notably the retroviruses.

Polymyositis develops over the months as compared to inclusion body myositis (IBM), which is a slowly progressive chronic myopathy developing in older individuals over a period of months to years with more severe symptoms. (3) Being an autoimmune disorder, polymyositis, a rheumatological disease, requires long-term treatment with glucocorticosteroids and immunosuppressive agents which are the mainstays of therapy for PM. The principal goals of therapy are to improve strength and improve physical functioning. Many patients require treatment for many years.

Although this is a rare disorder, polymyositis should be a part of the differential diagnosis of patients experiencing unexplained symptoms of muscle weakness because the failure to make a diagnosis can have a significant impact on the patient's quality of life due to severe complications. (4)

Epidemiology:

Polymyositis rarely presents in childhood and usually affects people above the age of 20 years. The chances of disease development are almost double in women than in men i.e female to male ratio is 2:1, which is exactly the opposite of IBM. PM can affect people of any age, but most commonly presents between the ages of 50 to 70. In the USA population, the rate of development of this autoimmune disorder is about 0.5 to 8.4 cases per 100,000 individuals. The overall prevalence of PM is 1 per 100,000. Having ethnic variation, it has been more commonly reported in Black individuals than in White ones. (5)

Etiology:

Polymyositis (PM) is an autoimmune disorder, result from abnormal activation of cytotoxic T lymphocytes (CD8 cells) and macrophages against muscular antigens as well as the strong extrafusal muscular expression of major histocompatibility complex class 1 causing damage to the endomysium of the skeletal muscles. (6)

Different cytokines, including interleukins, tumor necrosis factor (TNF), etc. play an important role in process of rhabdomyolysis. It mostly affects individuals already suffering from some kind of systematic disease such as viral infections, malignancies, or other autoimmune disorders. The usually responsible viruses for polymyositis are the retroviruses, human immunodeficiency virus (HIV) and HTLV1, as well as hepatitis C virus that possibly cause this inflammatory muscle degeneration by the endomysial damage leading to edematous swelling in addition to nodular mass formation in the myocytes. (7)

Coxsackievirus is another important reason for this autoimmune disorder due to the abnormal functioning of major histocompatibility complex (MHC) secondary to releasing of the cytokines after damaging the intima and endothelium of blood vessels. (8) Other important causative factor for polymyositis-induced rhabdomyolysis is an underlying malignancy such as lung carcinoma, genitourinary malignancy or lymphomas. The presence of polymyositis also increases the possibility of developing carcinoma in 2-5 years after the diagnosis of the case, especially non-Hodgkin lymphoma. It has the highest risk of development followed by both lung carcinoma and bladder carcinomas.

Other causes include the presence of certain HLA variants (A1, B8, DR3), the presence of another autoimmune disease such as celiac disease, and the use of some medications such as hydralazine, angiotensin-converting enzyme (ACE) inhibitors, procainamide, and antiepileptics due to their ability to act as a hapten. A study in US reported that 24% of patients on statin therapy developed polymyositis. (9)

Pathophysiology:

PM occurs by two ways: Direct damage as a result of the cellular immune response that develops through abnormal activation of cytotoxic T cells (CD8) and macrophages with some involvement of type B lymphocytes and dendritic cells. (10)

Indirectly, damage can happen due to releasing of inflammatory mediators in circulation by the cells such as cytokines and interleukins. A study reported a significant increase in pro-inflammatory cytokine IL-21, both in the muscle and serum of affected patients, along with the increasing of IL-21 receptors (IL-21R) in damaged muscle fibers in these patients. T helper type 1 (Th-1) response due to the release of cytokines (TNF, interferon-gamma, IL-12) as well as T helper type 17 (Th17) response due to its pro-inflammatory mediators (IL-17, IL-22, and IL-6) are other probable pathogenic mechanisms for causing polymyositis. (11)

In addition to causing direct damage, some certain cytokines such as IL-1alpha and IL-17 also upregulate the nuclear factor kappa B (NF-kappaB) signaling pathway to increase MHC class -1 expression. NF-kappaB also damages myofibrils by affecting the myocytes' differentiating ability negatively. (12)

Other potential pathological causes for polymyositis comprise damage to vascular endothelium leading to extravasation of the inflammatory mediators from circulation along with the involvement of humoral immune response depending on the presence of certain antibodies.

Diagnosis:

History and Physical examination:

The most important first step in diagnosing polymyositis in the early stage is to get a detailed history, including family history, medication history, and any antecedent infections.

The hallmark of polymyositis is a progressive disease with symmetrical involvement of girdle muscles (shoulder and pelvis muscles) and neck flexors that can be painful some times. (13) Hip extensors can also be involved in some patients making it difficult for them to climb stairs or to take posture change. Patients may complain of the inability of overhead abduction or to get up from the seated position. Disease progression to distal

muscles can result in abnormal fine movements such as writing, typing, or playing musical instruments. Constitutional symptoms including low-grade fever, anorexia, arthralgia, and weight loss may be present. Polymyositis can cause interstitial lung disease (ILD), especially in anti-Jo-1 positive individuals, presenting as shortness of breath and dry cough. (14) Other presenting complaints are chest tightness as well as exertional dyspnea as a result of restrictive cardiomyopathy, constipation, or bloating due to gastrointestinal involvement and tightening and discoloration of fingers due to Raynaud phenomenon.

In physical examination it is a must to get a complete motor and sensory examination of affected muscles. Although the sensory examination is usually normal in these patients, motor examination reveals a decrease in power of the affected portion depending on disease severity with loss of tendon reflexes in severe muscular atrophy. Patients with restrictive polymyositis can present with limited mobility of the truncal muscles, especially abnormal flexion that is called camptocormia. (15) The affection of nasopharyngeal muscles can result in nasal tone in speech. If polymyositis is associated with any malignancy, then features of that malignancy particular neoplasia can be seen e.g., lymphadenopathy in non-Hodgkin lymphoma. Skin rashes can also be found in the presence of other autoimmune disorders such as mixed connective tissue disorder. (16)

Evaluation:

The multi-modal approach consisting of (hematologic and serologic testing, imaging, electromyography, nerve conduction studies, and biopsy findings), is used to evaluate a patient with a suspected polymyositis. A complete blood count (CBC) can show an elevated lymphocytes count in the majority of the patients in addition to frequently thrombocytosis as well. (17) Erythrocyte sedimentation rate (ESR) can also be elevated as a result of chronic inflammation. Serum creatine kinase (CK) levels can be as high as up to fifty times the normal range (22 to 198 units/liter), indicating muscular damage due to chronic inflammation. It can be of great clinical use to monitor the progression of the disease by having serial examinations and CK monitoring. (18)

Multiple antibodies can be elevated in PM, such as a non-specific antinuclear antibody (ANA), which can be positive in around 33 % of the patients with polymyositis. If ANA turns out to be positive, then a specific antibody testing is done to confirm the diagnosis of PM, which is the anti-signal recognition particle (SRP) in the serum. The presence of anti-aminoacyl tRNA synthetases (ARS) antibodies can show the association of PM with an autoimmune syndrome known as the anti-synthetase syndrome. (19) This is characterized by a group of varying physical presenting features such as inflammation-induced myopathy, joint pain, Raynaud's phenomenon, and fibrotic lung disease. In the case of statin-induced PM, a unique 3-hydroxy-3-methylglutaryl coenzyme A reductase IgG immunoglobulin (anti- HMGCR) can be elevated. (20)

Almost all the patients with PM will have abnormal electromyography (EMG) findings such as varying amplitude and velocity of the membranous action potential, and fibrillation in potentials due to membrane irritability, etc. (21) A vital investigation to make a definitive diagnosis of myopathy is a magnetic resonance imaging (MRI) or EMG guided biopsy that shows perivascular and endomysial mononuclear infiltrates (cytotoxic T lymphocytes and macrophages) and areas of necrosis staining pink due to high eosin stain binding. (22)

Imaging studies such as MRI, computed tomography (CT) scan, or ultrasonography can be useful to locate an area of muscle damage and also to diagnose underlying malignancy. Whole-body magnetic resonance imaging is of utmost significance to exactly diagnose the damaged muscular area. (23)

If the patient presents with dysphagia, a barium swallow can be performed. In the case of lung disease, pulmonary function tests (PFTs) can be done. If PM has caused damage to cardiomyocytes, then an electrocardiogram (EKG) and echocardiography can be performed. (24)

Management and treatment:

Polymyositis is treated with a combination of different pharmacological and non-pharmacological modalities. Pharmacological treatment mainly includes corticosteroids. (25) Corticosteroids like prednisone are the first line of therapy for PM. The usual starting dose is 1 mg/kg/day of prednisone or its equivalent. This dose is usually maintained for the first 6-8 weeks. The steroids are tapered off gradually and not withdrawn suddenly. In a steroid responsive patient, the goal is to attain the lowest dose of steroids that will adequately manage the disease. In order to achieve this goal, steroid-sparing agents are necessary in most PM patients. The process of selecting steroid-sparing drugs is empirical, although the most commonly used are azathioprine (AZA) and methotrexate (MTX). (26) Cyclophosphamide, an immune-modulator, works efficiently, especially in patients with the involvement of the pulmonary interstitium. In the case of chronic refractory polymyositis, intravenous immunoglobulins (IVIG) can be used. A study showed improvement in around 70% of the patients after the use of IVIG. (27)

IVIG also shows significant improvement in patients having dysphagia due to esophageal involvement. Rituximab (RTX) is a monoclonal antibody against CD 20 positive B-cells, which causes depletion of these cells for 6 months or longer. The optimal dose of RTX in PM is unknown. One protocol is to use 375 mg/m², infused intravenously once a week for 4 weeks. Other therapies option include tacrolimus, a calcineurin inhibitor that has proven to be beneficial in patients having a refractory disease with simultaneous use of prednisolone. Mycophenolate mofetil has also been found to be useful in treating refractory cases of polymyositis. (28)

Patients with different systems involved must be evaluated by the concerned specialty e.g. cardiologist for cardiomyopathy, pulmonologist for ILD, a speech therapist for voice change, etc. Non-pharmacological treatment includes physical therapy of the affected muscles to prevent disuse atrophy. These patients must be advised to have supervised resistive strength training activities. These individuals should be advised to have a diet rich in proteins that help in muscle building. (29)

Complications:

Although polymyositis is a rare disease, it has been found to be associated with increased morbidity and mortality due to its associated comorbid conditions, e.g., the involvement of major vessels or gastrointestinal tract, etc. Patients with polymyositis have about 2.2% risk of having myocardial infarction as compared to the general population. (30) Patients with polymyositis are most likely to be diagnosed with cancer within the first year following the diagnosis of polymyositis, so age and gender-specific evaluation for malignancy should be done in all the patients with PM. According to a study, the presence of a high neutrophil/lymphocyte ratio in patients above the age of 60 years greatly increases the risk of having carcinoma of lung/bladder or non-Hodgkin lymphoma. (31)

Polymyositis affects the distal musculature of the esophagus in the late stage of disease in up to 70% of the patients leading to the inability to swallow, as well as regurgitation problems that can cause aspiration pneumonia. The involvement of the lungs can increase the mortality rate due to having an adverse impact on the quality of life. The presence of PM in the females of the child-bearing age group can result in a fetal loss in the case of active disease. (32)

PM can induce a hypercoagulable state in the plasma leading to the increased incidence of thromboembolism. (33) An increase in the risk of development of amyotrophic lateral sclerosis was also observed in a study in patients with PM. Osteoporosis risk has been found to be elevated in patients with PM. (34)

Prognosis:

Polymyositis, being a chronic disease, is associated with a grave prognosis in the long run. In addition to causing disability and affecting the quality of life of the patient, this

disease has also been found to be associated with a 10% mortality rate, especially in those who also develop cardiac dysfunction or malignant conditions. The majority of patients usually respond to steroid therapy. This disease has the worst prognosis in the patients having refractory disease, older females, Blacks, and patients having systematic involvement. (34)

Conclusion:

Polymyositis (PM) is one of the inflammatory myopathies, disorders characterized pathologically by the presence of inflammatory infiltrates in striated muscle. The principal clinical manifestation of PM is proximal muscle weakness. The cause of PM is unknown, but current evidence suggests that it is an autoimmune disorder. PM can affect people of any age, but most commonly presents between the ages of 50 to 70. PM is rarely seen in people younger than 20 years of age, and is twice as common among females than males. PM is more common in blacks than in whites. The overall prevalence of PM is 1 per 100,000. Muscle weakness may develop suddenly or more insidiously over a period of weeks to months. The classic symptom of PM is proximal weakness, which may manifest as difficulty holding the arms over the head, climbing stairs, or rising from a chair. Weakness of the striated muscle of the upper esophagus may result in dysphagia, dysphonia, and aspiration. The chest wall muscles may be affected, leading to ventilatory compromises. Involvement of cardiac muscle may lead to arrhythmias and congestive heart failure. Dermatomyositis (DM) is closely related to PM, and both are distinguished primarily by the occurrence of characteristic skin abnormalities in the former. PM may be associated with a variety of malignancies. PM may also occur as part of the spectrum of other rheumatic diseases like systemic lupus erythematosus and mixed connective tissue disease. Moreover, inflammatory myopathy may be caused by some drugs (procainamide, D-penicillamine), and viruses, most notably the retroviruses. Corticosteroids and immunosuppressive agents are the mainstays of therapy for PM. The principal goals of therapy are to improve strength and

improve physical functioning. Many patients require treatment for several years. The 5-year survival rate for treated patients is in the order of 95%. Up to one-third of PM patients may be left with some degree of residual muscle weakness.

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