

UNICORNS, DRAGONS, POLYMYOSITIS AND OTHER MYTHOLOGICAL BEASTS: THE TRUTH ABOUT POLYMYOSITIS

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Polymyositis is a commonly diagnosed condition in Neurology, Internal Medicine and Rheumatology.¹ The traditional diagnosis of polymyositis calls for presence of proximal muscle weakness, elevated creatinine phosphokinase, needle electromyography evidence of irritable myopathy and muscle biopsy features of an inflammatory myopathy with endomysial inflammation with cytotoxic T-cell and invasion of non-necrotic muscle fibers with inflammatory cells.² However, a number of cases have been diagnosed using only some of these criteria, most commonly proximal muscle weakness and elevated creatinine phosphokinase. A number of physicians, especially rheumatologists, often avoid muscle biopsies to establish a diagnosis of polymyositis. They depend on the **Bohan and Peter** criteria, introduced for the first time in 1975,³ prior to true recognition of inclusion body myositis.⁴ Through this talk I will provide evidence that the Bohan and Peter criteria are no longer appropriate for diagnosis of inflammatory myopathies and the time has come to use criteria that combine clinical, pathological and serological data to make a definitive diagnosis. Many such criteria have been proposed.⁵⁻⁸ Furthermore many diseases mimic polymyositis and need to be considered when making a diagnosis of polymyositis. Finally I will show evidence that polymyositis is much rarer than what would be apparent from the somewhat common diagnosis that we encounter day to day in clinical practice.

Bohan and Peter Criteria

In a seminal two-part review of the topic titled Polymyositis and Dermatomyositis, Anthony Bohan and James B. Peter, both from the University of California, Los Angeles, they set forth the diagnostic criteria for the diagnosis of polymyositis and dermatomyositis.^{3,9} This system was introduced before the entity of sporadic inclusion body myositis was fully described - even though it was reported for the first time in 1971 (actually the case described was a case of hereditary inclusion body myopathy),⁴ the first detailed description of what we now consider classic sporadic inclusion body myositis was not published till 1978.¹⁰ Thus this diagnostic classification does not take into consideration sporadic inclusion body myositis. The Bohan and Peter criteria defined five major criteria to define polymyositis and dermatomyositis: 1) symmetrical weakness of the limb-girdle muscles and anterior neck flexors, progressing over weeks to months, with or without dysphagia or respiratory muscle involvement; 2) muscle-biopsy evidence of necrosis of Type I and II fibers, phagocytosis, regeneration with basophilia, large vesicular sarcolemmal nuclei and prominent nucleoli, atrophy in a perifascicular distribution, variation in fiber size, and an inflammatory exudate, often perivascular; 3) elevation in serum of skeletal-muscle enzymes, particularly creatine phosphokinase and often aldolase, serum glutamate oxaloacetate and pyruvate transaminases, and lactate dehydrogenase; 4) electromyographic triad of short, small, polyphasic motor units, fibrillations, positive sharp waves and insertional irritability, and bizarre, high-frequency repetitive discharges; and 5) dermatologic features including a lilac discoloration of the eyelids (heliotrope) with periorbital edema, a scaly, erythematous dermatitis over the dorsum of the hands (especially the metacarpophalangeal and proximal interphalangeal joints, Gottron's sign), and involvement of the knees, elbows and medial malleoli, as well as the face, neck, and upper torso (this type of distribution is considered by many to be virtually pathognomonic of dermatomyositis). They defined confidence level as: 1) definite, consisting of three or four criteria (plus the rash) for dermatomyositis, and four criteria (without the rash) for polymyositis; 2) probable, comprising two criteria (plus the rash) for dermatomyositis, three criteria (without the rash), for polymyositis; and 3) possible, including one criterion (plus the rash) for dermatomyositis, and two criteria (without the rash) for polymyositis.

Limitations of the Bohan and Peter Criteria

A number of diseases would easily fulfill the possible or probable criteria for polymyositis using the Bohan and Peter criteria. For example a patient with Limb-Girdle Muscular Dystrophy type 2B with dysferlin mutations can easily fulfill the definite criteria for polymyositis (with inflammatory biopsy, elevated CK, myopathic EMG and proximal muscle weakness).¹¹ Similarly Late-Onset Pompe Disease (LOPD) will make the probable criteria easily (other than inflammatory changes on the biopsy).¹² Even patients with inclusion body myositis may fulfill the criteria for definite IBM early in their disease. About 20% of patients, especially female patients, with IBM may

have symmetric weakness and early on in the disease rimmed vacuoles may not be seen on the muscle biopsy.¹³ Some IBM patients may also respond briefly to immunosuppressive treatment, although Bohan and Peter discouraged use of steroid responsiveness (and now IVIG responsiveness) as diagnostic criteria.¹³

Even criteria for dermatomyositis may not be as sensitive. Heliotropic rash of the eyelids is now established as the most characteristic rash in dermatomyositis but the other skin rashes, including Gottron's papules, mechanic's hands, etc. can be seen in other forms of inflammatory myopathy including anti-synthetase syndrome, which is pathologically and serological very different from dermatomyositis, and overlap myositis, especially those associated with PM/Scl antibodies.^{6,14} Furthermore it is now well described that DM patients may have normal levels of CK (despite abnormal EMG and muscle biopsy).¹⁵ Certain forms of DM may have an entirely different type of skin rash, for instance forms of DM associated with antibodies to Melanoma Differentiation Antigen-5 (MDA-5) may not have muscle weakness and have a skin rash that is different with ulcerating lesions on the tips of the fingers.⁶ Also up to 6% of DM patients may not have skin rash (*dermatomyositis sans dermatitis*).¹⁶ Five distinct antibodies are associated with DM (Mi-2, NXP-2, SAE, MDA-5 and TIF- γ). Each of these has direct influence on disease phenotype and prognostication. For instance antibodies to TIF- γ predict a malignancy either one-year prior to or after the discovery of the myositis.¹⁷ NXP-2 antibodies predict calcinosis, while MDA-5 predicts an amyopathic disease with very high risk of interstitial lung disease.⁶

Newer Entities that Need to be Considered when Diagnosing Polymyositis

There are a number of conditions that had not been described in 1975 when Bohan and Peter criteria were described. These include anti-synthetase syndrome, which most authorities now consider a separate entity from DM and PM;^{6,14} necrotizing autoimmune myopathies (NAM), such as those associated with Signal Recognition Particle (SRP) antibodies^{18,19} and antibodies to HMGCoA reductase (HMGCR antibodies),²⁰⁻²² and sporadic inclusion body myositis.¹⁰

SRP antibody associated necrotizing myopathy is a severe necrotizing myopathy that is associated with a severe muscle weakness, high CK and poor response to immunosuppressive therapy.^{18,23} There is now evidence that the myositis may respond to intravenous rituximab.²⁴ HMGCR antibody associated necrotizing autoimmune myopathy may also be a severe necrotizing myopathy, associated with markedly elevated CK values and requires often 3-drug regimen to control the disease.^{21,25} There is some emerging data however, that suggests that intravenous immunoglobulins (IVIG) may be useful as a single agent to control the disease.²⁶

Anti-synthetase syndrome encompasses a group of myositides where antibodies to aminoacyl t-RNA synthetase are found.¹⁴ The most classic of this is Jo-1 myositis, where the clinical features are that of proximal weakness and elevated CK. However muscle pathology shows a very characteristic pathology of predominantly perimysial pathology, with inflammation, fragmentation of perimysial connective tissue, preservation of intramuscular capillaries (in sharp contrast to DM) and pathognomonic intranuclear Actin inclusions.^{27,28} A very high risk of developing interstitial lung disease exists. Skin lesions include mechanic's hands, Gottron's papules and other skin rashes. A seronegative erosive arthritis may co-exist.¹⁴

How rare is polymyositis and how do we refine the diagnosis of polymyositis?

A number of papers have now reviewed the issue of how rare polymyositis is.^{13,16,29} Most of these studies have shown that at long term follow up (5-10 years) over 90% of these cases diagnosed with polymyositis were found to have an alternate diagnosis. Common alternate diagnoses included inclusion body myositis, overlap syndrome (including PM/Scl syndrome) and necrotizing autoimmune myopathies.^{16,29} This realization that polymyositis is really rare was editorialized and equated polymyositis to unicorns and dragons and other mythical beasts.³⁰

Serology: Newer studies have focused on increasing sensitivity to diagnosis of other diagnoses that may mimic Polymyositis. Obviously the role of serology has really vastly increased our ability to stratify different diseases. In addition to the myositis specific antibodies that are already described above, a couple of new antibodies are important to mention here.³¹ HMGCR antibodies are associated with necrotizing autoimmune myopathies and usually predict a severe myopathy with high CK in patients often exposed to statin class anti-cholesterol medications.²¹ However, this antibody has also been seen in adult patients who have never been exposed to statins or in pediatric patients who obviously have not been treated with statins.³² HMGCR antibody associated myositis may look like polymyositis and would have met the criteria for definite polymyositis in the Bohan and Peter criteria but is a very different disease.

Serum NT5c1A antibodies are the new biomarker in inclusion body myositis and has remarkably high specificity (upwards of 94%) in patients with muscle weakness for the diagnosis of IBM.³³⁻³⁵ Even though this antibody can be found in patients with lupus and Sjögren's disease, no muscle weakness was seen in those patients.^{33,35} Thus the presence of this antibody in these disorders may just represent presymptomatic disease. The antibody is known to be present many years prior to their diagnosis of IBM;³⁶ we recently diagnosed a patient with IBM who had NT5c1A antibodies present in his serum 14 years prior to his definitive diagnosis. Furthermore our group has shown that seropositivity for the NT5c1A antibody predicts a more severe motor phenotype, with greater need for assistive devices, such as walker and wheelchair, and higher frequency of dysphagia.³⁷ This was recently reaffirmed in a European study; their study also showed reduced life expectancy in the seropositive IBM patients.³⁴ Seronegative patients had higher incidence of proximal limb weakness. Seropositive patients have significantly more cytochrome oxidase negative fibers.³⁴ There is also a suggestion that seropositive patients may have less rimmed vacuoles on muscle biopsy.³⁸

Myopathology: Muscle biopsy plays an important role in differentiating polymyositis from IBM and NAM. Even though endomysial inflammatory cell infiltrate with cytotoxic T-cells is the hallmark for PM, it can be seen in IBM. In fact without the presence of rimmed vacuoles PM is indistinguishable from IBM on light microscopy.³⁹⁻⁴² MHC class 1 upregulation is common to both.⁴¹ Rimmed vacuoles may not be seen in all cases and may not be present early on in the disease.¹³ Female patients have less rimmed vacuoles and may present with more symmetric weakness.¹³ Furthermore seropositive patients have less rimmed vacuoles than seronegative patients. Additional stains such as cytochrome oxidase staining and staining for autophagy marker p62 really distinguishes IBM from PM and provides high sensitivity and specificity of diagnosis of IBM in cases of rimmed vacuolar as well as non-rimmed vacuolar myopathies.⁴³ Presence of COX negative fibers provides a sensitivity and specificity of 86% for diagnosis of IBM when rimmed vacuoles are present and sensitivity of 78% and specificity of 91% when rimmed vacuoles are not present for a diagnosis of IBM.⁴³ Similarly presence of p62 immunostaining provides a sensitivity of 87% and specificity of 86% for diagnosis of IBM when rimmed vacuoles are present and a sensitivity of only 22% but specificity of 91% for diagnosis of IBM when rimmed vacuoles are not seen.⁴³

Newer studies have questioned the specificity of muscle fiber invasion of non-necrotic muscle fibers in PM.¹³ When followed long term, an overwhelming majority individuals who had muscle fiber invasion manifested clinical features consistent with diagnosis of IBM. Rimmed vacuoles on the initial muscle biopsy was seen in only 60% of the cases and men tended to have more rimmed vacuoles than women. Thus muscle biopsy diagnosis of IBM should not solely depend on demonstration of rimmed vacuoles on muscle biopsy, and should take into consideration additional features, such as muscle fiber invasion of non-necrotic fibers, cytochrome oxidase negative fibers and presence of p62 or TDP-43 immunostaining in rimmed vacuolar or non-rimmed vacuolar muscle fibers.⁴⁴

Time has come to abandon Bohan and Peter criteria for diagnosis of inflammatory myositis

I have demonstrated that reliance on Bohan and Peter criteria for diagnosis of inflammatory myositis leads to over diagnosis of PM and is no longer adequate given the advances in the field of inflammatory myositides since 1975. A number of new classification systems have been proposed that have used either phenotypic characteristics or more important used either serology or myopathology or sometimes all three (clinical, serological and myopathological) to classify inflammatory myositides.⁵⁻⁸ A number of workshops under the auspices of the European Neuromuscular Center (ENMC) have tried to address this issue;⁴⁵⁻⁴⁸ at this time concordance amongst these criteria is low.⁴⁹ Despite this there continues to be a heavy reliance on the Bohan and Peter criteria and this criteria is still used to determine subject eligibility in clinical trials in inflammatory myositides.

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