Journal of Investigative Medicine High Impact Case Reports
Volume 10: 1–5

DOI: 10.1177/23247096221074589
journals.sagepub.com/home/hic
SAGE

Polymyositis Presenting With Nontraumatic Rhabdomyolysis and Dysphagia: A Case Report

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Abstract

Idiopathic inflammatory myopathies (IIMs) are a rare, heterogeneous group of diseases with a characteristic clinical presentation consisting of muscle inflammation and weakness. They often present with accompanying extra-muscular findings, most notably in the skin, lungs, and joints. Inflammatory myopathies are also identified by their characteristic laboratory abnormalities, including a 10- to 50-fold increase in creatinine kinase, elevated liver enzymes, and characteristic electromyography and magnetic resonance imaging findings. Distinct autoimmune markers and clinical phenotypes have advanced our understanding of IIMs and have led to the recognition of 5 distinct entities, each with its unique pathophysiology, autoimmune markers, and clinical features. While autoimmune panels and muscle biopsies help clinicians distinguish one entity from the other, their sensitivity and specificity vary. Of the various inflammatory myopathies, polymyositis remains the most elusive. Often, the diagnosis is ultimately made by combining clinical findings and laboratory data. As our case report illustrates, clinicians must use this constellation of data to initiate treatment for suspected polymyositis despite negative autoimmune panels and negative muscle biopsy.

Keywords

polymyositis, seronegative, idiopathic inflammatory myopathy, rhabdomyolysis, Epstein-Barr

Introduction

Idiopathic inflammatory myopathies (IIMs) are a rare, heterogeneous group of diseases characterized by proximal muscle weakness. Collectively, it is estimated that the incidence rates for the IIMs are between 4.27 and 7.89 per 100 000 person-years, whereas the prevalence rates range from 9.54 to 32.74 cases per 100 000 individuals.[1] While the pathogenesis of IIMs is not fully elucidated, it is thought that genetic predispositions, such as single-nucleotide polymorphisms in B-cell scaffolding proteins and certain human leukocyte antigen types, combined with environmental triggers precipitate the disease. Dysregulation of the innate and adaptive immune system characterized by B-cell activation and T-cell infiltration is thought to underlie the pathogenesis of IIMs. Other measures of inflammatory activity, such as type 1 interferons, elastase to polymorphonuclear monocyte ratio, monocyte chemoattractant protein-1, and transforming growth factor-B1 concentration, have been positively correlated with disease activity and severity.[2]

Since its introduction in 1975, the Bohan and Peter classification criteria remain widely used. It consists of ruling out all other forms of myopathies and the following criteria:

1. Symmetrical, progressive weakness of limb-girdle muscles with or without dysphagia and respiratory muscle weakness;
2. Muscle biopsy evidence of myositis;
3. Elevation of serum levels of muscle-associated enzymes (eg, CK, LDH, transaminases, aldolase);
4. Electromyography (EMG) findings such as short, small, low-amplitude polyphasic motor unit potentials, fibrillation potentials even at rest, and bizarre high-frequency repetitive changes;
5. The characteristic rash of dermatomyositis.

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Received September 9, 2021. Revised December 29, 2021. Accepted January 2, 2022.

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It further stratifies polymyositis (PM) and dermatomyositis (DM) disease probability into 3 categories: definite, probable, and possible. For PM, the presence of the first 4 classification criteria yields a definite diagnosis, the presence of 3 criteria carries a probable diagnosis, while the presence of the first 2 diagnostic criteria carries a possible diagnosis. The sensitivity of these diagnostic criteria has been reported to be anywhere between 94% and 98% but its specificity is lower, ranging from 29% to 55%.[3,4] Based on the above criteria, IIMs were then classified into 5 groups: primary idiopathic PM, primary idiopathic DM, IIMs associated with malignancy, childhood IIMs associated with vasculitis, and IIMs associated with collagen vascular diseases.

Since the inception of these classification criteria, the paradigm for the classification, diagnosis, and treatment of these diseases has changed with the identification of myositis-specific antibodies (MSAs) and myositis-associated antibodies (MAAs). The presence of MSAs and their association with distinct clinical and histological patterns have proposed 5 distinct entities: DM, PM, necrotizing autoimmune myositis, anti-synthetase syndrome-overlap myositis, and inclusion body myositis.[3,4] Nonetheless, IIMs remain difficult to diagnose. Antibody detection in inflammatory myopathies varies, with any known autoantibody present in 60% to 80% of cases and a MSA present in 40% to 50% of cases.[5-8] The sensitivities of muscle biopsies, considered the gold standard, have been reported to be anywhere from 45% to 85%.

Polymyositis remains a diagnosis of exclusion. With the refinement of classification criteria, the existence of PM was brought into question as many previously identified PM cases would now be classified as one of the other 4 entities based on clinical features and histological and autoantibody patterns; however, PM has been validated as its own distinct phenotype.[7-11] This report validates PM as its own distinct entity, using the European League Against Rheumatism/American College of Rheumatology Classification Criteria (EULAR/ACR) to make the diagnosis.

Case Report

A 19-year-old male with a past medical history of asymptomatic COVID-19 in October 2020 first presented to the Emergency Department with complaints of 3 weeks of generalized myalgias, lower extremity proximal, lower muscle weakness, nausea, vomiting, and left-lower quadrant pain. Transaminases were elevated, alanine aminotransferase (ALT) 961 IU/L, aspartate aminotransferase (AST) 1563 IU/L, as well as alkaline phosphatase (ALP) 226 IU/L and total bilirubin (1.4 mg/dL). During that admission, liver ultrasound revealed biliary sludge vs small gallstones without bile duct dilation and no liver abnormalities. The patient was diagnosed with acute hepatitis, presumably due to an Epstein-Barr virus (EBV) infection based on positive IgM and IgG EBV titers from an outside clinic 1 week prior. Although a negative monospot test and a normal WBC differential were noted, the patient was discharged with improving transaminases and symptomatic improvement. However, the patient returned 6 days after discharge with similar but worsening symptoms, now including dysphagia. Laboratory studies revealed an elevated creatinine kinase (CK) of 38 290 units/L, leukocytosis (20.13 K/μL) without lympho/monocytosis, elevated transaminases (ALP 253 IU/L, ALT 484 IU/L, AST 1123 IU/L), lactic acidosis (2.7 mmol/L), elevated C-reactive protein (1.2 mg/dL), and erythrocyte sedimentation rate (58 mm/h). A head computerized tomographic (CT) scan revealed a 6.5 cm fluid collection in the retropharyngeal space near C2-C4. Abdominal/pelvic CT scan revealed loss of the normal signal of the thigh muscles, suggestive of myositis, as well as pooling of contrast in the renal pelvis, suggesting renal disease. The fluid collection in the pharynx was drained and empiric antibiotic coverage was initiated, although cultures were negative. On hospital day 2, the patient developed acute hypoxic respiratory failure with altered mental status requiring intubation and, on day 7, developed an acute kidney injury with oliguria (CK 44 330 units/L, BUN 38 mg/dL, creatinine 3.4 mg/dL) requiring hemodialysis (Figure 1). Subsequent head magnetic resonance imaging (MRI) and lumbar puncture were unremarkable. Eventually, a nasogastric tube was required due to swallowing impairment.

An extensive infectious disease workup for infectious, myositis, and rheumatological assays were all negative (Table 1). Core muscle biopsy of right thigh showed normal muscle fibers and was negative for EBV, fungi, and mycobacterium via EBV early RNA probe, and Grocott's methenamine silver and acid-fast bacillus (AFB) stains, respectively.

Treatment was initiated with intravenous methylprednisolone (1 g/daily) and mycophenolate mofetil the dose rapidly increased to 1.5 g twice daily. The patient's clinical picture significantly improved after treatment initiation. The patient was successfully extubated on hospital day 15 and hemodialysis was discontinued on day 18. The patient's swallowing improved on day 25 allowing removal of the nasogastric tube. He began tolerating a regular, solid-food diet on day 33. Lower extremity weakness, though still pronounced, continued to improve with physical therapy. The patient was discharged to an inpatient physical rehabilitation facility on prednisone (20 mg, daily) and mycophenolate mofetil (1500 mg, twice a day) after an extended hospital course of 37 days.

Discussion

The diagnosis and classification of PM and other IIMs have been a source of discussion for the past several decades, with multiple proposed classification criteria.[4,7-10] Polymyositis can be a complex and difficult diagnosis due to its overlapping features with other IIMs and autoimmune diseases.

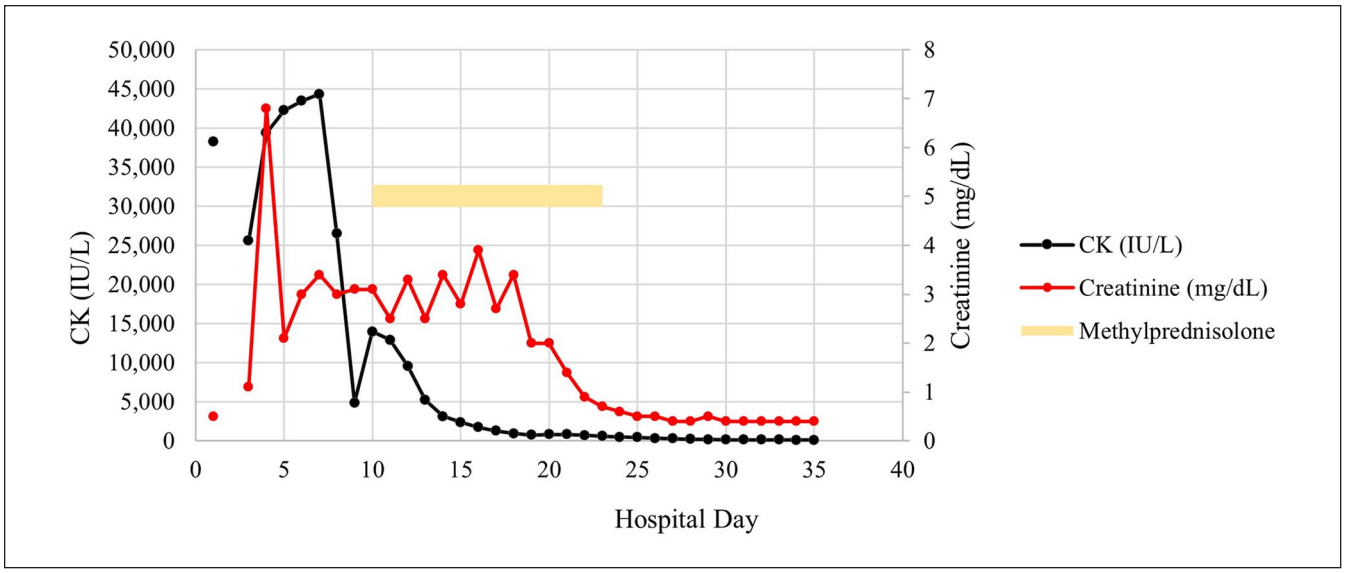

Figure 1. Trending CK enzymes, creatinine, and steroid treatment during hospital stay.
Abbreviation: CK, creatinine kinase.

Table 1. Infectious, Myositis, and Rheumatological Assays.

Infectious	Myositis	Rheumatological
Coccidoides	Anti-Mi-2	Rheumatoid factor
Coxsackie B	Anti-threonyl-tRNA-synthetase [PL-7]	Sjogren Syndrome [anti-SSA/SSB]
Cytomegalovirus	Anti-alanyl-tRNA synthetase [PL-12]	Anti-histidyl tRNA synthetase [Jo-1]
Enterovirus	Anti-Ku	Anti-U1 small nuclear ribonucleoprotein [Sm/RNP]
Epstein Barr	Anti-glycyl-tRNA synthetase [EJ]	Anti-smooth muscle
Hepatitis A/B/C	Anti-isoleucyl-tRNA synthetase [OJ]	Antimitochondrial antibodies
Mycobacterium tuberculosis	Anti-signal recognition particle [SRP]	
	Antimitochondrial M2 antibodies	

Most classification criteria emphasize the following: (1) muscle weakness, (2) muscle biopsy, (3) EMG findings suggestive of myositis, and (4) elevation of CK and other muscle enzymes. Although most IIM classification criteria recommend the presence of an inflammatory muscle biopsy, muscle biopsy may be normal due to patchy inflammation, as was the case with our patient.[12] Nonetheless, it is still possible to diagnose and classify PM without a positive muscle biopsy. Using the Peter and Bohan criteria, our current case would carry a possible PM diagnosis. Using the EULAR/ACR criteria, the IIMs calculator (available at http://www.imm.ki.se/biostatistics/calculators/iim/), we arrive at a composite score of 7.6 out of 20, indicating a definite diagnosis of IIM. Using the algorithm provided by the same classification criteria, PM is identified as the IIM subclassification.[13] Both MSAs and MAAs were negative, highlighting their limited utility and re-emphasizing the importance of clinical criteria in diagnosis.

While the pathophysiology of PM is not fully understood, genetic susceptibility, external insults, and dysregulation of both innate and adaptive immunity are thought to underly its pathogenesis. Polymyositis is characterized by infiltration of the endomysium by mononuclear cells, predominantly CD8+ T cells. These cells target the major histocompatibility complex 1 (MHC-1) of non-necrotic muscle fibers. Cytokines such as type-1 interferons, tumor necrosis factor α, and interleukin-1 induce the aberrant expression and upregulation of MHC-1 complexes in the muscle sarcolemma, which do not otherwise express MHC-1 complexes. Muscle biopsies will typically show CD8-MHC-1 complexes characteristic of PM. Polymerase chain reaction (PCR) analysis of clonally expanded CD8+ T cells demonstrated conserved sequences in the antigen-binding region, suggesting that monocellular infiltration and muscle inflammation are antigen-driven. Autoantigens are thought to be presented in the MHC-1 complexes to CD8+ T cells; these cells bind the overexpressed MHC-1 complexes and inject perforin and granzyme granules into the muscle cells leading to myocyte cell death and muscle fiber breakdown.[14,15] Several viruses such as human T lymphocytic virus 1 (HTLV-1), human

Table 2. Traumatic and Nontraumatic Causes of Rhabdomyolysis.[28]

	Hypoxic	Physical	Chemical	Biological
Extrinsic	Carbon Monoxide, Cyanide Poisoning	Hypo/Hyperthermia, Burns, Electrocution, Hypo/Hyperthermia	Environmental Toxins, Drugs, Substance Abuse	Infections, Organic Toxins
Intrinsic	Compartment Syndrome, Compression, Immobilization, Vascular Occlusion	Exertion, Seizures, Status Asthmaticus, Agitation, Malignant Hyperthermia	Electrolyte Disorders	Idiopathic Inflammatory Myopathies, Endocrinopathies, Mitochondrial Myopathies

immunodeficiency virus (HIV), hepatitis C, coxsackievirus,[16] and EBV[16-21] have been implicated in this dysregulated immune response, although the precise mechanism remains unknown and a causal link has not yet been established. Although EBV was suspected to be the etiology for this patient's PM, EBV RNA was not noted in biopsied muscle tissue and EBV DNA was undetectable via PCR.

The interaction between CD8+ T cells/MHC-1 complexes can lead to severe inflammation and extensive muscle damage; as such, it is not uncommon to see CK counts go up 10 to 50 times higher than baseline and other muscle enzymes (eg, ALT, AST, aldolase) elevated. Our patient was admitted with severely elevated CK and myoglobinuria, suggesting extensive muscle breakdown leading to rhabdomyolysis, acute tubular necrosis, and renal insufficiency. The CT scan also showed loss of normal signal in thigh muscles and mild inflammation adjacent to iliopsoas muscles. While MRI is considered the preferred method for visualizing muscle inflammation in PM and other IIMs, we note here that CT scans can show utility for visualizing muscle inflammation.[22]

Myositis was thought to be a rare cause of rhabdomyolysis.[23] However, recent studies estimate the incidence of rhabdomyolysis in IIMs at 20%.[24,25] A recent case series of 475 patients demonstrated 27 patients with IIMs presented with rhabdomyolysis; of these, 21 were identified as having PM.[26] While substance abuse, drugs, and trauma account for most of the rhabdomyolysis cases, any disease process causing muscle inflammation/breakdown can potentially lead to rhabdomyolysis (Table 2), including autoimmune diseases. This report illustrates the need to keep IIMs as part of the differential diagnosis in rhabdomyolysis.[23-28]

Normally, the intracellular gradient of Sodium (Na^+) and Calcium (Ca^2+) ions is maintained at low concentrations through the action of Na/K-ATPase pumps, as well as ion exchangers and transporters. Regardless of whether the initial insult is traumatic, genetic, biochemical, or inflammatory, the pathomechanism of rhabdomyolysis converges: a disruption of the cell membrane leads to an influx of sodium and calcium ions into the cytoplasm, disrupting energy production and activating calcium-dependent proteases and phospholipases, which further damage myocytes and disrupt membrane integrity. This disruption allows the release of intracellular metabolites and proteins into the bloodstream. Of these metabolites and proteins, myoglobin is associated with renal insult and renal failure, which has been estimated to occur in 14% to 46% of rhabdomyolysis cases.[23-28] While normally bound to plasma proteins, destruction of just 100 g of muscle tissue can be enough to overwhelm the plasma-binding proteins and can subsequently lead to precipitation of myoglobin in the glomerular filtrate, leading to tubular occlusion and renal failure. Diagnosis of rhabdomyolysis is typically done through measuring CK levels, with levels >1000 typically used to make the diagnosis. As CK increases, the severity of rhabdomyolysis increases as well as the probability of acute renal failure, with one study estimating an overall risk of acute renal failure of about 70% when serum CK levels are $>15\,000$.[28]

In summary, we report a case of nontraumatic rhabdomyolysis due to IIM. Despite the absence of associated antibodies and confirmatory biopsy, the patient responded well to aggressive therapy for PM.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Verbal informed consent was obtained from the patient for their anonymized information to be published in this article.

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