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Dermatomyositis: A Review of Diagnosis and Classification Criteria

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ABSTRACT

Dermatomyositis is an autoimmune disorder affecting skin and muscle and one of the subgroups of idiopathic inflammatory myopathy (IIM). Dermatomyositis is more common among women than men and it may occur in adults or children. This disease is also related to malignancy and internal organ involvement. However, around 20% of cases are present without muscle damage. The presence of myositis-specific autoantibodies may help in diagnosis and predict the prognosis of the disease. Early diagnosis of the disease is foremost required for appropriate management. Furthermore, validated diagnostic and classification criteria are important in the clinical setting and studies.

Keywords: autoimmune, classification criteria, dermatomyositis, diagnosis

INTRODUCTION

Dermatomyositis (DM) is a systemic autoimmune disorder characterized by skin rash and muscle damage. DM is an idiopathic disease with multifactorial causes such as genetic, environmental, and immunologic factors. This disease is more common among women compared to men. The cutaneous manifestation usually coexists with proximal muscle weakness in classical DM. Traditionally, DM is considered idiopathic inflammatory myopathies (IIM) which have the general presentation of muscle weakness[1]. However, around 20% of cases demonstrate absent muscle weakness, making diagnosing DM challenging. The latter is referred to as clinically amyopathic dermatomyositis (CADM). Several proposed diagnostic and classification criteria have been made to distinguish the disease, yet those criteria have not been validated. Apart from that, several studies focusing on muscle histology and clinical findings are clearly not specific to DM. The importance of early diagnosis is because classical DM and CADM have similar risks of developing systemic involvement (interstitial lung disease (ILD) and malignancy commonly)[2]. Moreover, ILD is the most common cause of morbidity and mortality in these patients. Approximately, around 35-45% of patients with polymyositis or dermatomyositis may develop ILD. Since the disease includes autoimmune diseases, 50-70% of cases have circulating myositis-specific autoantibodies [3-4]. The presence of specific autoantibodies also contributes to risk stratification of organ involvement[2]. Therefore, this study will give an in-depth explanation of the diagnostic and classification criteria of DM and the prognosis of the disease.

EPIDEMIOLOGY

A population-based study from Olmsted County, Minnesota, showed the incidence and prevalence of dermatomyositis and all its subtypes from 1976 to 2007. The overall incidence was 9.63 per 1,000,000 (95% confidence interval [CI], 6.09-13.17). Meanwhile, the age-and-sex-adjusted incidence of CADM was 2.08 per 1,000,000 (95% CI, 0.39-3.77)[5]. There were 28% and 17% of patients diagnosed with cancer and lung disease respectively among the subjects.

Dermatomyositis is two times more prevalent in women compared to men, and it may occur in children and adults. Dermatomyositis has bimodal age distribution, occurring at 5-14 and 45-64 years of life [2]. Another study in Taiwan utilizing the data from a health insurance dataset showed the mean age at diagnosis of DM was 44±18.3 years old. The study identified the total number of cases of DM between 2003-2007 which showed the annual incidence of DM was 7.1 per 1,000,000 (95% confidence interval [CI] 6.6-7.6). The peak incidence occurred at 50-59 years old. Among them, there were 13.7% of cases diagnosed with cancer [6]. Moreover, the similarity in terms of the annual incidence of DM in Southeast Norway showed that the incidence ranged from 6-10% per 1,000,000 with the peak incidence of 50-59 years [7].

ETIOPATHOLOGY

Dermatomyositis is known as an idiopathic immune-mediated disease with presenting muscle weakness and skin rash because several cases involve myositis-specific autoantibodies. Nonetheless, the etiopathogenesis of dermatomyositis is still debatable[4]. The risks of developing dermatomyositis are multifactorial which include genetics, immunology, and environmental factors. Polymorphism of human leukocyte antigen (HLA) is believed to increase the risk of developing the disease. The first identified allele was HLA -B8 harbored in 75% of juvenile dermatomyositis patients. Several high-risk haplotypes of HLA include HLA-A*68, HLA-DRB1*0301, HLA-DQA1*0104, HLA-DRB1*07, DQA1*05, and DQB1*02[1-2]. Besides, the innate and adaptive immune response also contributes to the pathogenesis of DM. This evidence is proven by the histological and molecular features of the disease. The direct inflammatory effect is caused by the activity of CD4+, CD8+ T cells, B cells, dendritic cells, and macrophages while the indirect effect involves several cytokines such as interferons (IFNs), interleukins (ILs), and tumor necrosis factors (TNF)[8]. High level of interferon (IFN) can induce DM-autoantigen such as MDA5 which then accounts for humoral response producing autoantibodies[2]. Another study also mentioned the contribution of the humoral immune response toward the damage of muscle capillaries and endothelial cells of arterioles causing vasculopathy. The direct attack is initiated through the activation of completer factor-3 (C3) that forms C3b and C4b. This event is followed by the formation of membrane attack complex (MAC) which deposits in the vascular wall and causes inflammation. Hypoxic injury occurs and causes muscle atrophy which, over time, the muscle undergoes necrosis and degeneration. Furthermore, viral infections such as coxsackie B virus, enterovirus, and parvovirus infection may trigger the disease. Several drugs such as antineoplastic drugs, antibiotics (penicillin, sulfonamide, isoniazid), NSAIDs (diclofenac), and radiation could contribute to disease development[4]. Another theory also mentions the nonimmune pathophysiology of DM which involves the role of endoplasmic reticulum stress. This event occurs due to the upregulation of MHC class 1 or other proteins that leads to the activation of inflammatory nuclear factor kappa B (NF-KB), mitochondrial dysfunction, and elevated reactive oxygen species. This will contribute to the weakness symptoms of DM patients. Moreover, another study also suggests the initiation of DM happens in genetically predisposed persons with insults from environmental factors. Environmental factors such as infection, malignancy, and UV exposure may induce endoplasmic reticulum stress, increase interferons (IFN) production, and activate immune responses[2,9].

CLINICAL FEATURES

The signs and symptoms of dermatomyositis include cutaneous and extracutaneous manifestations. The skin rash characteristic of dermatomyositis is erythematous to

violaceous patches in the affected skin. People with darker skin types have more subtle and overlooked rashes. The rash usually manifests before, right after, or at the same time with muscle weakness. It is commonly accompanied by pruritus, scale, and skin tightness which can occur in sun-exposed or non-sun-exposed areas. The lesions may develop into deep ulcers, atrophy, and scarring. Patients may complain of crawling and tingling sensation along with the rashes [4]. The pathognomonic cutaneous signs of DM include Gottron papules, Gottron sign, V-Neck sign, Heliotrope sign, shawl sign, and Holster sign. Gottron papule is erythematous and violaceous papules on the extensor area of the metacarpophalangeal and interphalangeal joints. The erythematous macules or patches appear on the elbows/knees (Gottron signs), upper front chest (V-neck signs), upper back (shawl signs), and upper eyelid (Heliotrope signs)[1,8]. Holster sign is ill-defined papules coalescing into plaques with scales on the lateral side of the thigh. The vasculopathy signs include livedo reticularis, telangiectasia, and ulceration. The hyperkeratotic lesion with ill-defined erythematous papules and horizontal lines on the lateral and palmar side of the second and third digits causes the appearance of a mechanic's hand in DM patients. Other manifestations include nail changes and alopecia[2].

The extracutaneous manifestations involve several organs such as pulmonary, musculoskeletal, gastrointestinal, and cardiovascular systems. Musculoskeletal involvement causes symptoms such as polyarthritis, muscle weakness, joint swelling, and arthralgia of small joints. Myalgia and muscle tenderness may occur in 30% of cases. Despite the presence of myalgia, muscle weakness and evidence of muscle enzyme elevation may not be present in 20% of cases[1-2].

DIAGNOSIS

The diagnosis of dermatomyositis is based on clinical findings and supporting examination. Several supporting examinations that could be done in the diagnosis of DM include muscle enzymes, autoantibodies, electromyographic studies, imaging studies, histopathology of skin and muscle, and investigation for malignancy[2]. The term clinically amyopathic dermatomyositis (CADM) is used clinically by physicians to describe patients with classic cutaneous manifestation for more than 6 months without signs or symptoms of myositis. Two subcategories are derived from CADM: amyopathic and hypomyopathic dermatomyositis. Those terms are defined based on the results of further imaging (muscle enzymes, electromyography, and MRI). If the patient has amyopathic DM, the results of those tests are normal. Meanwhile, patients with hypomyopathic DM have at least one abnormal result[2,4].

MUSCLE ENZYMES

Several muscle enzymes such as creatine kinase, aldolase, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) should be tested in order to evaluate muscle injury[1-2]. Early cases of DM usually show elevated levels of muscle enzymes, but decreased levels in mid to late disease progression. This event might be the result of perifascicular muscle atrophy and fibrosis. Sometimes, only the creatine kinase or aldolase will be elevated in DM patients. Moreover, several conditions may increase enzyme levels which must be considered in testing muscle enzymes such as previous history of strenuous physical activity or history of hepatic injury. Another additional examination such as γ-Glutamyl transferase needs to be done to differentiate muscle injury due to hepatic dysfunction. Re-evaluation also may be required 10-14 days after previous strenuous activity. Testing muscle enzymes is useful to guide further diagnostic studies. Moreover, muscle enzymes sometimes appear in advance of the appearance of muscle weakness[2].

AUTOANTIBODIES

Since DM is an autoimmune disease, there are several autoantibodies present in DM patients, called myositis-specific autoantibodies (MSA). Myositis-specific autoantibodies are helpful in establishing the diagnosis, determining the prognosis, and predicting the internal organ involvement of DM patients[2]. These MSAs include antisynthetase autoantibodies (Jo-1, PL-7, PL-12, EJ, OJ, KS, Zo), anti-Mi-2 (directed against helicase protein), anti-SAE (small ubiquitin-like modifier activating enzyme), anti-TIF1-γ (transcription intermediary factor), anti-NXP 2 (nuclear matrix protein 2), anti-MDA5 (melanoma differentiation-associated gene 5) and are present approximately in 30% of DM and polymyositis cases. In the US cohort study, the sensitivity of MSA detection is 80-85% for diagnosis of DM. Previously, the first discovered MSA was an autoantibody to Mi-2, a nuclear helicase protein. The presence of anti-Mi-2 has been associated with good prognosis, lower risk of interstitial lung disease (ILD) and malignancy, and better response to steroids[3]. Besides, the most common myositis-specific autoantibody found in dermatomyositis is Aminoacyl-transfer (t) ribonucleic acid synthetase (also known as an antisynthetase antibody). One of the most prevalent antisynthetase antibodies is anti-Jo which is associated with antisynthetase syndrome (comprised of fever, inflammatory arthritis, Raynaud's phenomenon, and ILD)[9-10]. Several techniques to identify MSA include immunofluorescence, enzyme-linked immunosorbent assay (ELISA), immunoblotting, and immunoprecipitation [9]. Immunoprecipitation is the gold standard for the detection of MSA[10].

ELECTROMYOGRAPHIC STUDIES (EMG)

Electromyography can detect muscle abnormality in early disease of dermatomyositis and is present in 70-90% of cases. However, the abnormality found in EMG results is not specific to dermatomyositis because it may also be seen in other muscle diseases. The sensitivity of EMG decreases along with the late progression of the disease[2]. The classic triad of EMG findings in myositis include small amplitude, short duration, polyphasic motor unit potentials; fibrillations and positive sharp waves; and complex repetitive discharges. Cases of clinically amyopathic DM may not give abnormal results in electromyographic studies[1].

IMAGING STUDIES

Magnetic resonance imaging (MRI) can differentiate between damage or steroid-induced myopathy and active myositis. Moreover, this imaging is sensitive and noninvasive to help distinguish muscle pathologic processes such as edema, inflammation, calcification, atrophy, and fibrosis may also be distinguished using MRI. The typical finding of myositis is muscle edema which appears hyperintense on T2-weighted images. Increased signal intensity indicates muscle inflammation, necrosis, and degradation within the muscle. Chest x-rays in DM patients may help screen for early signs of interstitial lung disease (ILD). If the result is abnormal, high-resolution computer tomography (HRCT) should be done to detect further suggestive findings of ILD such as fibrosis, nodules, linear opacities, honey-combing, and consolidation[1-2].

HISTOPATHOLOGICAL FINDING

Muscle biopsy is rarely done if the patient has obvious signs and symptoms of myositis which are approved by the laboratory, EMG, or MRI results, because it can give false-negative results. The nature of the patchy distribution of inflammation might make it challenging to determine the site of muscle biopsy [2]. If the test is necessary, muscle biopsy should be obtained from the weak muscle that can be determined from MRI results[1]. The typical findings of muscle biopsy include perifascicular atrophy (atrophy of muscle fibers especially around the periphery of fascicle), perivascular and

perimysial inflammatory infiltrate (consisting of B cells, CD4+ T cells, macrophages, dendritic cells, and plasma cells), and microangiopathy (deposit of membrane attack complex in the endomysial capillary wall)[1-2]. A skin biopsy can be obtained if the patients have no muscle weakness. The typical results of cutaneous biopsy include cell-poor interface dermatitis, increased dermal mucin, perivascular infiltrate, and ectasia. Cell-poor interface dermatitis consists of basal cell vacuolization and lymphocytes at the dermal-epidermal junction (DEJ). The perivascular infiltrate is a specific characteristic of dermatomyositis which is absent in cutaneous lupus erythematosus[2].

MALIGNANCY INVESTIGATION

Dermatomyositis is associated with internal malignancy in 10-20% of cases[2]. Usually, malignancy might occur during the first 5 years of disease onset with the possibility of various types of cancer. The screening of malignancy should be age and sex appropriate. The types of cancer vary from solid tumors or hematopoietic cancers[1]. The most common types of solid tumors include breast, prostate, lung, ovarian, colorectal, gastric, pancreatic, and nasopharyngeal cancers. Several DM-specific autoantibodies may relate to an increased risk of having malignancy such as anti-TIF1-γ and anti-NXP2 autoantibodies. Several examinations may be done including colonoscopy, pap smear, mammography, urine analysis, transvaginal ultrasound, and fecal examination. Moreover, tumor markers may also be helpful in detecting malignancy (e.g. CA-125 for ovarian cancer)[2,4].

CLASSIFICATION CRITERIA

Idiopathic inflammatory myopathy (IIM) is a group of myopathy diseases with similar clinical, laboratory, and pathological features. One of the subgroups includes dermatomyositis[8]. Several classification criteria have been proposed and implemented to distinguish each disease for clinical and laboratory studies such as Bohan and Peter classification (1975), Tanimoto classification (1995), Targoff et al. classification (1997), Dalakas criteria (2003), and The European Neuromuscular Center (ENMC) criteria (2004). However, there are some limitations to the existing criteria such as vague exclusion criteria, unclear definition of DM cutaneous manifestation, failure to incorporate autoantibodies, failure to include all subgroups of the disease, and not properly validated [1,11]. Apart from classification criteria, diagnostic criteria are used to establish the diagnosis of a particular disease. Usually, diagnostic criteria are obtained from cohort studies. However, classification criteria sometimes are inappropriately used to make a diagnosis. As of now, the validated classification criteria do not yet exist. However, the most current and well-developed criteria for IIM was published by the European League Against Rheumatism and the American College of Rheumatology (EULAR/ACR) in 2017 with a more detailed definition of each criterion and higher sensitivity and specificity compared to previous classification criteria. The EULAR/ACR criteria provide sensitivity and specificity of 97% and 82% respectively. The accuracy becomes higher if muscle biopsy is included, 93% and 88% respectively[12].

Table 1. Classification Criteria of the 2017 EULAR/ACR for adult and juvenile IIM

Variable	Score	
	No muscle biopsy	With muscle biopsy
Age of onset of first symptoms ≥ 18 and < 40 years	1.3	1.5
Age of onset of first symptoms ≥ 40 years	2.1	2.2
Muscle weakness		
Objective symmetric weakness, usually progressive, of the proximal upper extremities	0.7	0.7
Objective symmetric weakness, usually progressive, of the proximal lower extremities	0.8	0.5
Neck flexor are relatively weaker than neck extensor	1.9	1.6
In the legs, proximal muscles are relatively weaker than distal muscle	0.9	1.2

Cutaneous manifestation		
Heliotrope rash	3.1	3.2
Gottron's papules	2.1	2.7
Gottron's sign	3.3	3.7
Other clinical manifestations		
Dysphagia or esophageal dysmotility	0.7	0.6
Laboratory examinations		
Anti-Jo1 autoantibody present	3.9	3.8
Elevated serum levels of CK or LDH or ASAT/AST/SGOT or ALAT/ALT/SGPT	1.3	1.4
Muscle biopsy features – presence of		
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibres		1.7
Perimysial and/or perivascular infiltration of mononuclear cells		1.2
Perifascicular atrophy		1.9
Rimmed vacuoles		3.1
Cited from [11]. Anti-Jo1, anti-histidyl-tRNA synthetase; CK, creatine kinase; LDH, lactate dehydrogenase; ASAT/AST/SGOT, aspartate aminotransferase; ALAT/ALT/ SGPT, alanine aminotransferase [11]		

Each score obtained from the classification criteria corresponds to the probability of the disease, with or without a muscle biopsy. The patients are defined as "possible", probable", or "definite" cases of IIM if the patients have a probability of less than 50%, 55-75%, and more than 90%, respectively[1]. According to the score results, the score of 5.5 without biopsy and 6.7 with biopsy will categorize patients as probable IIM while score of more than 7.5 without biopsy and more than 8.7 with biopsy is considered as definite IIM[12].

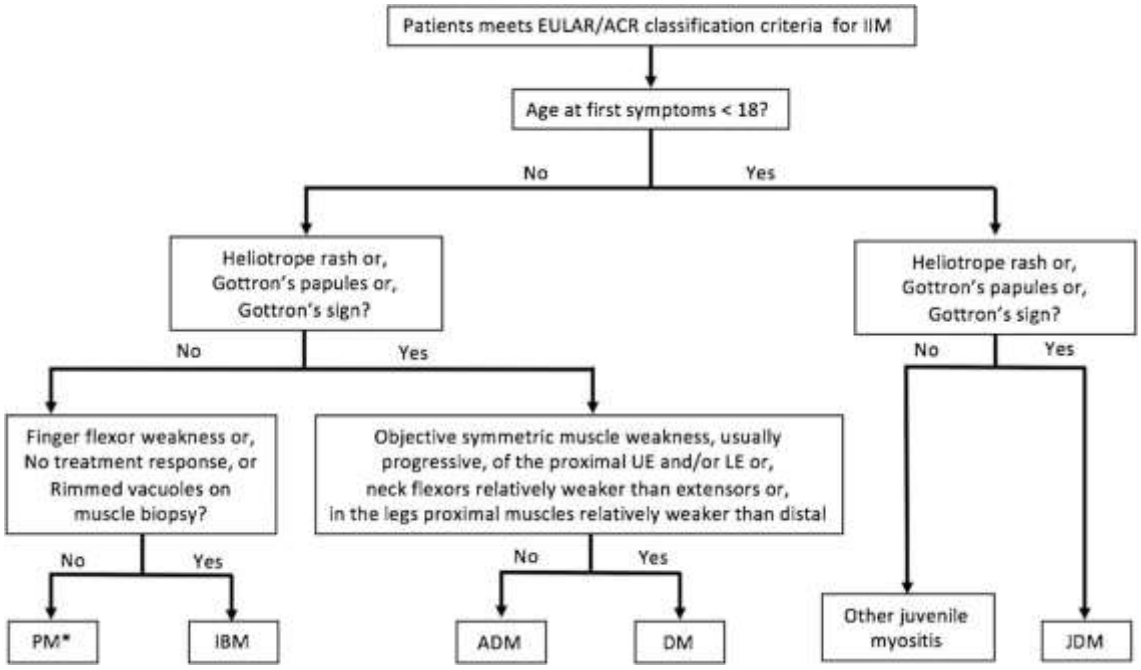

Figure 1. Classification tree of the 2017 EULAR/ACR classification criteria [11] *The PM subgroup includes immune-mediated necrotizing myopathies (IMNM). PM, polymyositis; IBM, inclusion body myositis; ADM, amyopathic dermatomyositis; DM, dermatomyositis; JDM, juvenile dermatomyositis.

Once the patient meets the classification criteria and the probability, the subtypes can be identified through a classification tree as seen in Figure 1. Even though the EULAR/ACR criteria are more well-developed, there is a limitation. Despite heterogeneous diseases included in IIM, some rare disease groups (e.g., immune-mediated necrotizing myopathy (IMNM), hypomyopathic DM, and juvenile PM) may not have enough patients that have only one MSA, anti-Jo1. It is possible that other MSAs may likely replace anti-Jo1 as variables. Thus, further revision using cohort data might take into account to include more data on other MSAs [11].

CONCLUSION

Dermatomyositis is an autoimmune disorder presenting with cutaneous and musculoskeletal manifestations. It is one of the subgroups of idiopathic inflammatory myopathy (IIM). Since IIM includes several diseases that share similar clinical and pathological features, it becomes challenging to distinguish each subgroup of disease. The 2017 EULAR/ACR classification criteria is developed and has been partly validated by many multispecialty experts that help to group each disease for the purpose of clinical studies and trials. The gold standard for making the diagnosis of dermatomyositis is based on the physician's clinical decision which is supported by additional supporting examination.

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