Serum Muscle Enzymes, Muscle Pathology and Clinical Muscle Weakness: Correlation in Thai Patients with Polymyositis/Dermatomyositis

WORAWIT LOUTHRENOO, M.D.*, NUANANONG WEERAYUTWATTANA, M.D.*,
NIRUSH LERTPRASERTSUKE, M.D.**, WARAPORN SUKITAWUT, B.Sc.*

Abstract

The clinical correlation between serum muscle enzymes, muscle pathology and muscle weakness was studied in 100 Thai patients (22 males and 78 females) with polymyositis (PM) and dermatomyositis (DM). Their mean ± SD age and duration of disease were 45.0 ± 13.9 years and 6.3 ± 13.4 months, respectively. There was idiopathic PM in 37 cases, idiopathic DM in 13, PM/DM associated with malignancy in 5 and PM associated with connective tissue disease in 45. Serum muscle enzymes including creatine phosphokinase, lactate dehydrogenase and aspartate aminotransferase were elevated in 87 per cent, 92 per cent, and 82 per cent of cases, respectively. Abnormal electromyographic findings that were compatible with inflammatory myopathy were found in 76 per cent of cases. Seventy-seven per cent had an abnormal muscle biopsy that was consistent with polymyositis. There was a significant correlation between serum muscle enzymes and muscle pathology ($p < 0.01$). The degree of muscle weakness correlated better with the degree of muscle destruction ($p = 0.01$) than the degree of muscle inflammation ($p = 0.03$). The erythrocyte sedimentation rate showed no correlation with serum muscle enzymes, muscle pathology or muscle weakness.

Key word : Polymyositis, Dermatomyositis, Serum Muscle Enzymes, Pathology, Clinical Correlation

LOUTHRENOO W, WEERAYUTWATTANA N, LERTPRASERTSUKE N, SUKITAWUT W
J Med Assoc Thai 2002; 85: 26-32

* Division of Rheumatology, Department of Medicine,
** Department of Pathology, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand.

Polymyositis (PM) and dermatomyositis (DM) are inflammatory muscle diseases characterized by symmetric proximal muscle weakness, myalgia, arthralgia/arthritis, elevated serum muscle enzymes and skin rashes[1,2]. The disease can occur alone or in association with connective tissue diseases or malignancies. In more severe cases, it can involve deglutition, respiratory and cardiac musles resulting in dysphagia, and respiratory and cardiac failure[3,4]. The clinical features and laboratory findings in patients with PM/DM overlap with those of other autoimmune, neurologic diseases and metabolic myopathies[5]. Studies have shown that immunologic mechanisms play an important role in the pathogenesis of the disease[5].

Although the clinical features and outcome of patients with PM/DM have been extensively reported[3,4,6-11], the clinical correlation between muscle weakness, serum muscle enzymes abnormalities and pathological findings of the muscle is limited[10-12]. The purpose of our study was to determine the correlation between clinical muscle weakness, serum muscle enzymes and muscle pathology in Thai patients with PM/DM.

MATERIAL AND METHOD

The medical records were reviewed of patients diagnosed with PM, which were seen at the Division of Rheumatology, Department of Medicine, Faculty of Medicine, Chiang Mai University from January 1987 to December 1999. The diagnosis and classification of PM followed the description of Bohan and Peter[1,2]. With this criteria, patients were classified further into 4 subgroups: group 1, idiopathic PM; group 2, idiopathic DM; group 3, PM/DM associated with malignancies; and group 4, PM associated with connective tissue diseases. Patients diagnosed with juvenile PM/DM or infectious myositis were excluded. All patients were seen by a rheumatologist (WL).

During the study period, there were 163 patients clinically diagnosed with PM/DM. One hundred and twenty-eight patients had a muscle biopsy, which was performed within 1 week from the elevation of serum muscle enzymes being documented. However, only 102 muscle specimens were available for review. Two specimens that showed granulomatous inflammation with the possibility of tuberculous myositis were excluded and, therefore, only 100 specimens were available for this study.

The demographic characteristics and clinical presentation of these 100 patients were reviewed. Blood results, which included complete blood counts, erythrocyte sedimentation rate (ESR), serum muscle enzymes [creatinine phosphokinase (CPK), lactate dehydrogenase (LDH) and aspartate aminotransferase (AST)], serum electrolytes, renal and liver function tests, rheumatoid factors, and an antinuclear antibody test at the time of presentation, were recorded. Results of the electromyographic (EMG) study were noted when available.

The muscle power was divided into 6 grades as follows: Grade 5 = normal muscle power; Grade 4 = slight weakness of the muscle with ability to move against resistance; Grade 3 = muscle weakness with ability to move against gravity, but not able to move against resistance; Grade 2 = muscle weakness with ability to move only without resistance; Grade 1 = muscle weakness with inability to move, but visible muscle contraction seen; and Grade 0 = muscle weakness without visible muscle contraction.

In order to categorize the degree of myositis better, the muscle pathology was graded according to the degree of muscle inflammation (or infiltration of inflammatory cells in the muscle tissue), and the degree of muscle fiber destruction. A semiquantitative 5-point scale (Grade 0-4) was used to grade the degree of inflammation and destruction. Grade 0 (normal), 1 (very mild), 2 (mild), 3 (moderate) and 4 (severe) referred to 0, < 10 per cent, 10-24 per cent, 25-50 per cent, and > 50 per cent of cellular infiltration and of muscle fiber destruction, respectively (Fig. 1 A-D). All of the muscle biopsy specimens were reviewed by NL.

Statistical analysis

The data was analyzed by using the SPSS version 9.0 statistical program (SPSS Inc., Chicago, Illinois, USA). The Spearman's correlation was used to determine the correlation between variables. A p-value of < 0.05 was considered to have a statistically significant difference.

RESULTS

There were 78 females and 22 males, with a mean $\pm$ SD age and duration of symptoms of 45.0 $\pm$ 13.9 and 6.3 $\pm$ 13.4 months, respectively prior to the diagnosis of myositis being made. The clinical diagnosis was divided into group 1, 37 cases;

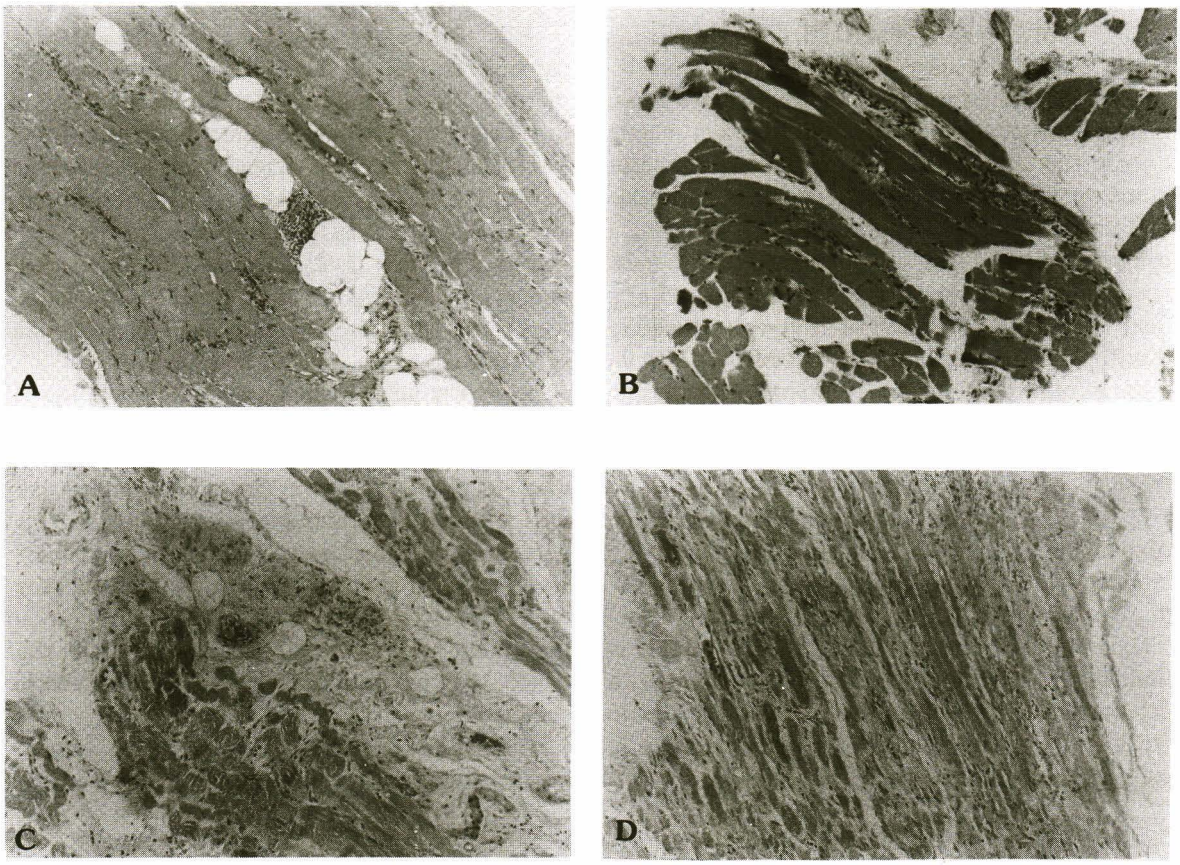

Fig. 1. Muscle biopsy showing various degrees of inflammation and destruction. A, degree of inflammation +1 and degree of destruction +1; B, degree of inflammation +2 and degree of destruction +2; C, degree of inflammation +3 and degree of destruction +4; D, degree of inflammation +4 and degree of destruction +4.

group 2, 13; group 3, 5; and group 4, 45 (scleroderma in 22 cases, systemic lupus erythematosus in 16, mixed connective tissue disease in 6, and polyarteritis nodosa in 1). Proximal muscle weakness was documented in 93 cases, of which 56 also had neck muscle weakness. Forty-nine cases had dysphagia. Myalgia, arthralgia and arthritis were seen in 31, 49, and 20 cases, respectively. Raynaud's phenomenon was seen in 32 cases, 26 of which were in group 4. EMG was performed in 38 cases, which showed an abnormal finding that was consistent with the inflammatory myositis in 29 cases (76.3%). Sixteen of 52 (30.8%) and 63 of 91 (69.2%) patients tested positive for rheumatoid factor and antinuclear antibody, respectively. Details of the clinical features and laboratory findings according to the disease group are shown in Table 1.

A mean ± SD value of serum muscle enzymes including CPK, LDH and AST were 2,058.2 ± 3115.0 U/L (normal 0-195), 720.3 ± 430.2 U/L (normal 113-246), and 175.8 ± 190.3 U/L (normal 3-37), respectively. The CPK, LDH and AST were elevated in 87, 92 and 82 cases, respectively. The CPK was normal in 13 cases, of which 4 had an abnormal muscle pathology that was consistent with myositis. The CPK was elevated 10 times greater than normal in 25 cases, of which 5 patients presented a normal muscle biopsy. Seventy-four per cent had elevated ESR (> 20 mm/h) with a mean ± SD ESR of 37.4 ± 20.4 mm/h.

Seventy-seven muscle biopsy specimens showed changes that were compatible with myositis. Details of the severity of inflammation and destruction, according to the disease group, are

Table 1. Clinical and laboratory features of patients with PM/DM related to classification group.

	Group 1	Group 2	Group 3	Group 4
Number of patients (%)	37	13	5	45
Sex M:F	10:27	4:9	2:3	6:39
Mean ± SD age (range)	45.6 ± 11.8	41.9 ± 13.1	46.4 ± 16.6	45.3 ± 15.7
Presenting features				
Weakness n (%)	35 (94.6)	12 (100.0)	5 (100.0)	41 (91.1)
Rash (%)	-	13 (100.0)	4 (80.0)	11 (24.4)
Myalgia (%)	11 (29.7)	7 (53.8)	-	13 (28.9)
Arthralgia (%)	14 (37.8)	5 (38.5)	-	30 (66.7)
Arthritis (%)	9 (24.3)	-	-	11 (24.4)
Dysphagia (%)	18 (48.6)	6 (46.1)	3 (60.0)	22 (48.8)
Raynaud's phenomenon (%)	5 (13.5)	1 (7.6)	-	26 (57.7)
Cardiac involvement (%)	5 (13.5)	3 (23.1)	-	10 (22.2)
Pulmonary involvement (%)	8 (21.6)	2 (15.4)	-	13 (28.8)
Mean ± SD CPK (u/L)	2,778 ± 3,295	3,196 ± 4,487	574 ± 464	1,302 ± 2,405
ANA positive (%)	16/32 (50)	8/11 (72.7)	3/5 (60.0)	36/43 (83.7)
RF positive (%)	7 /20 (35)	1/8 (12.5)	0/1 (0)	8/23 (34.8)
EMG abnormal (%)	14/16 (87.5)	3/4 (75.0)	1/1 (100.0)	12/17 (70.6)

Table 2. Degree of muscle inflammation and destruction according to patients group.

Degree of severity	Inflammation				Destruction			
	Group I (n = 37)	Group II (n = 13)	Group III (n= 5)	Group IV (n= 45)	Group I (n = 37)	Group II (n =13)	Group III (n = 5)	Group IV (n = 45)
0	13	6	2	26	10	3	2	16
1	3	-	1	1	-	-	-	3
2	7	2	2	8	3	3	2	13
3	6	2	-	6	7	1	1	4
4	8	3	-	4	17	6	-	9

shown in Table 2. Cellular infiltration composed mainly mononuclear cells in 73 specimens, and polymorphonuclear cells in 4. These 4 specimens were from patients who had had a disease duration of 1, 3, 12 and 12 months, respectively. Muscle fiber atrophy was noted in 25 cases. Vasculitis was seen in 14 specimens as follows: group 1, 2 and 4 in 2, 3 and 9 cases, respectively. Of the 9 patients in group 4 with vasculitis in their biopsies, 7 were systemic lupus erythematosus and 2 were scleroderma.

Table 3 shows the correlation between serum muscle enzymes (CPK, LDH and AST), ESR, muscle pathology, and muscle weakness. There was a significant correlation between the three serum muscle enzymes ($p < 0.01$). The level of these 3 serum enzymes also showed a significant correlation with muscle pathology ($p \leq 0.01$). Surprisingly, serum LDH and AST, but not CPK, correlated well with the degree of muscle weakness ($p < 0.01$). The degree of muscle weakness correlated more with muscle destruction than the degree of muscle inflammation ($p = 0.01$ *vs* 0.03, respectively). The ESR showed no correlation with serum muscle enzymes, muscle pathology and the degree of muscle weakness. Although the same pattern of correlation was also found in the subgroup analysis of group 1 and group 4, the correlation diminished in group 2 and group 3 (data not shown).

DISCUSSION

The presenting features of our patients: symmetric proximal muscle weakness, elevation of

Table 3. Correlation (r) between serum muscle enzymes, muscle pathology, ESR and muscle power.

LDH	0.592					
	(<0.01)					
AST	0.431	0.759				
	(<0.01)	(<0.01)				
ESR	-0.164	0.009	0.150			
	(0.33)	(0.96)	(0.40)			
Inflammation	0.376	0.286	0.265	-0.048		
	(<0.01)	(<0.01)	(0.01)	(0.78)		
Destruction	0.371	0.287	0.356	-0.046	0.690	
	(0.01)	(0.01)	(0.01)	(0.78)	(0.01)	
Muscle power	-0.193	-0.265	-0.262	0.077	-0.221	-0.302
	(0.06)	(0.01)	(0.01)	(0.64)	(0.03)	(0.01)
	CPK	LDH	AST	ESR	Inflammation	Destruction

( ) = p value

serum muscle enzymes, rashes, arthralgia and myalgia, were similar to many previously reported[3,6-10,12,13]. The 50 per cent incidence of dysphagia might reflect more severity in this group of patients. The authors found an incidence of Raynaud's phenomenon in 32 per cent of cases, of which 80 per cent were in group 4. The incidence of abnormal EMG in 76 per cent of cases, abnormal muscle biopsy in 77 per cent, positive RF test in 31 per cent and positive ANA test in 69 per cent was similar in number to that previously reported.

In this study, a significant correlation was found between the 3 serum muscle enzymes (CPK, LDH and AST), muscle pathology and muscle weakness. The degree of muscle weakness correlated more with the degree of muscle destruction than the degree of muscle inflammation. Interestingly, 13 of the patients had normal CPK with abnormal muscle pathology. Twenty-five had an elevation of more than 10 times normal, but 5 of these cases had normal muscle histopathology. The level of CPK could be normal in patients with PM, particularly in those with a long standing disease and significant muscle atrophy[6,11,13,14]. This might not correlate with the degree of muscle weakness and muscle pathology[10,11]. The reason for this discrepancy was not clear. This might be because myositis in PM is a diffuse process and the biopsy was not taken at the inflammatory site, or the level of CPK, which usually decreases to normal 3-4 weeks before the clinical improvement of muscle power, was document. However, CPK is generally accepted as a hallmark of myositis, and is used to follow the response to the treatment.

Although 74 per cent of the patients had elevated ESR, it did not show any correlation with serum muscle enzymes, muscle pathology or the degree of muscle weakness. There is some controversy about the usefulness of ESR in PM. Several studies showed that ESR had no correlation with the degree of severity of the disease and could not be used to predict the treatment outcome[4,6,10], but some found that ESR was helpful[9]. The present results agree with the former.

Even though the histopathology of myositis has been well described, the scoring system to categorize the degree of myositis has rarely been mentioned[10,12]. In this study, the authors developed a new pathological system to assess the degree of myositis. The degree of myositis was divided into 2 components, the degree of inflammation (as indicated by the degree of cellular infiltration) and the degree of muscle destruction (as indicated by the degree of muscle fiber destruction). It was found that this scoring system is simple, and easy to use. The pathological scores correlated well with the degree of elevation of serum muscle enzymes and muscle weakness. Therefore, this pathological scoring system is not only useful for grading the severity of the disease, but might also be advantageous as a follow-up for predicting the outcome. The present finding that the degree of muscle weakness correlated well with the degree of muscle fiber destruction was in line with previous observations[13]. This finding differed from others who found no correlation between the degree of muscle weakness and the degree of muscle necrosis[6,10,12]. The degree of muscle inflammation and des-

truction tended to be more severe in group 1 than in group 4 in this study, which was similar to that of Kalovidouris et al[12].

Despite the clinical features of PM and DM being similar, there is evidence suggesting that these 2 diseases have different immunopathogenesis[15]. DM is believed to be the result of humoral mediated immune response, as evidenced by the deposition of membrane attack complement within capillaries. This leads to muscle ischemia and necrosis, microinfarcts and perivasicular atrophy in the histopathology. The inflammatory cells infiltrate perivascularly, with an excess of B lymphocytes over T lymphocytes[16]. In contrast, PM is believed to be the result of cellular mediated immune response, as evidenced by the presence of T lymphocytes (predominantly CD8 cells) within muscle fasicles, and the non-necrotic muscle fibers are injured by cytotoxic T-cells[16-19]. Unfortunately, the antigenic stimulus for the above evidence is not known.

The authors found that vasculitis was more common in group 4. This might reflect the high proportion of SLE and scleroderma in the patients studied. This high proportion of SLE was similar to those of and Nadji et al[7] and Koh et al[9]. The presence of vasculitis was not a predominant histopathological finding in PM/DM and did not correlate with clinical features[12].

To conclude, the authors have developed a simple muscle histopathology scoring system for PM/DM. The scoring system showed that serum muscle enzymes, and the degree of muscle weakness correlated well together. The degree of muscle weakness correlated better with the degree of muscle destruction than the degree of inflammation. Histopathology of the muscle might help to predict the outcome of treatment.

(Received for publication on September 10, 2001)

REFERENCES

1. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med 1975; 292: 344-7.
2. Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). N Engl J Med 1975; 292: 403-7.
3. Benbassat J, Gefel D, Larholt K, Sukenik S, Morgenstern V, Zlotnick A. Prognostic factors in polymyositis/dermatomyositis. A computer-assisted analysis of ninety-two cases. Arthritis Rheum 1985; 28: 249-55.
4. Medsger TA, Robinson J, Masi AT. Factors affecting survivorship in polymyositis. A life table analysis of 124 patients. Arthritis Rheum 1971; 14: 249-58.
5. Wortman RL. Inflammatory diseases of muscle and other myopathies. In: Ruddy S, Harris ED, Sledge CB, editors. Kelly's textbook of rheumatology. 6th ed., Philadelphia: WB Saunders, 2001: 1273-96.
6. Bohan A, Peter JB, Bowman RL, Pearson CM. Computer-assisted analysis of 153 patients with polymyositis and dermatomyositis. Medicine 1977; 56: 255-86.
7. Nadji A, Davatchi F, Akbarian M, et al. Polymyositis and dermatomyositis (PM/DM) in Iran. Analysis of 139 cases. APLAR J Rheumatol 1999; 2: 105-8.
8. Akkasilpa S, Tumrasvin T, Deesomchok U. Clinical features of polymyositis/ dermatomyositis in Chulalongkorn Hospital. Chula Med J 1995; 39: 723-31.
9. Koh ET, Seow A, Ong B, Ratnagopal P, Tjia H, Chng HH. Adult onset polymyositis/dermatomyositis: Clinical and laboratory features and treatment response in 75 patients. Ann Rheum Dis 1993; 52: 857-61.
10. De Vera R, Bradley WG. Polymyositis: its presentation, morbidity and mortality. Brain 1975; 98: 637-66.
11. Riddoch D, Morgan-Hughes JA. Prognosis in adult polymyositis. J Neurol Sciences 1975; 26: 71-80.
12. Kalovidouris AE, Stoesz E, Muller J, Kimes T, Brandt KD. Relationships between clinical features and distribution of mononuclear cells in muscle of patients with polymyositis. J Rheumatol 1988; 15: 1401-6.
13. Dalakas MC. Polymyositis, dermatomyositis and inclusion-body myositis. N Engl J Med 1991; 325: 1487-98.
14. Bohlmeyer TJ, Alan HB, Perryman MB. Evaluation of laboratory test as a guide to diagnosis and therapy of myositis. Rheum Dis Clin North Am 1994; 20: 845-57.
15. Hilton-Jones D. Inflammatory muscle diseases. Curr Opin Neurol 2001; 14: 591-6.

16. Arahata K, Engel AG. Monoclonal antibody analysis of mononuclear cells in myopathies. I: Quantitation of subsets according to diagnosis and sites of accumulation and demonstration and counts of muscle fibers invaded by T cells. Ann Neurol 1984; 16: 193-208.
17. Engel AG, Arahata K. Monoclonal antibody analysis of mononuclear cells in myopathies. II: Phenotypes of autoinvasive cells in polymyositis and inclusion body myositis. Ann Neurol 1984; 16: 209-15.
18. Arahata K, Engel AG. Monoclonal antibody analysis of mononuclear cells in myopathies. IV: Cell-mediated cytotoxicity and muscle fiber necrosis. Ann Neurol 1988; 23: 168-73.
19. Arahata K, Engel AG. Monoclonal antibody analysis of mononuclear cells in myopathies. V: Identification and quantitation of T8+ cytotoxic and T8+ suppressor cells. Ann Neurol 1988; 23: 493-9.

ความสัมพันธ์ระหว่างระดับเอ็นซัยม์กล้ามเนื้อ พยาธิสภาพของกล้ามเนื้อ และอาการอ่อนแรงของกล้ามเนื้อในโรคกล้ามเนื้ออักเสบ/โรคผิวหนังและกล้ามเนื้ออักเสบในคนไทย

วรวิทย์ เลาห์เรณู, พ.บ., นวลอนงค์ วีระยุทธวัฒนะ, พ.บ.*, นิรัชร์ เลิศประเสริฐสุข, พ.บ.**, วราพร สุชีตาวุธ, วท.บ.**

ได้ศึกษาความสัมพันธ์ระหว่างระดับเอ็นซัยม์กล้ามเนื้อ พยาธิสภาพกล้ามเนื้อ และอาการกล้ามเนื้ออ่อนแรงในโรคกล้ามเนื้ออักเสบ/โรคผิวหนังและกล้ามเนื้ออักเสบ ในคนไทยจำนวน 100 ราย (เพศชาย 22 ราย เพศหญิง 78 ราย) ค่าอายุและระยะเวลาที่มีอาการเฉลี่ยเท่ากับ 45.0 ± 13.9 ปี และ 6.3 ± 13.4 เดือน ตามลำดับ เป็นโรคกล้ามเนื้ออักเสบที่ไม่ทราบสาเหตุ 37 ราย โรคผิวหนังและกล้ามเนื้ออักเสบที่ไม่ทราบสาเหตุ 13 ราย โรคกล้ามเนื้ออักเสบ/โรคผิวหนังและกล้ามเนื้ออักเสบที่พบร่วมกับโรคมะเร็ง 5 ราย และโรคกล้ามเนื้ออักเสบที่พบร่วมกับโรคเนื้อเยื่อเกี่ยวพัน 45 ราย ระดับเอ็นซัยม์ ได้แก่ creatine phosphokinase, lactate dehydrogenase และ aspartate aminotrasnsferase มีค่าเพิ่มขึ้นร้อยละ 87, 92 และ 82 ตามลำดับ ตรวจพบคลื่นไฟฟ้ากล้ามเนื้อผิดปกติและพยาธิสภาพกล้ามเนื้อผิดปกติเข้าได้กับโรคกล้ามเนื้ออักเสบ ร้อยละ 76 และ ร้อยละ 77 ตามลำดับ พบความสัมพันธ์ที่ชัดเจนระหว่างระดับเอ็นซัยม์กล้ามเนื้อและความผิดปกติทางพยาธิสภาพกล้ามเนื้อ ($p < 0.01$) อาการกล้ามเนื้ออ่อนแรงมีความสัมพันธ์กับความรุนแรงที่กล้ามเนื้อถูกทำลายทางพยาธิสภาพ ($p = 0.01$) มากกว่าความรุนแรงจากกล้ามเนื้ออักเสบ ($p = 0.03$) ไม่พบความสัมพันธ์ระหว่างอัตราเม็ดเลือดแดงตกตะกอน (erythrocyte sedimentation rate) กับระดับเอ็นซัยม์กล้ามเนื้อ ลักษณะทางพยาธิสภาพ และอาการอ่อนแรง

คำสำคัญ : กล้ามเนื้ออักเสบ, ระดับเอ็นซัยม์กล้ามเนื้อ, พยาธิวิทยา, ความสัมพันธ์

วรวิทย์ เลาห์เรณู, นวลอนงค์ วีระยุทธวัฒนะ, นิรัชร์ เลิศประเสริฐสุข, วราพร สุชีตาวุธ
จดหมายเหตุทางแพทย์ ฯ 2545; 85: 26-32

* หน่วยโรคข้อและรูมาติสซั่ม, ภาควิชาอายุรศาสตร์,
** ภาควิชาพยาธิวิทยา, คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่, เชียงใหม่ 50200