

Dermatomyositis without Creatine Kinase Elevation

A Poor Prognostic Sign

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Serum muscle enzyme levels are usually elevated in patients with untreated polymyositis and dermatomyositis. Creatine kinase is the muscle enzyme most often used to diagnose inflammatory myopathies. Seven patients with dermatomyositis and normal creatine kinase levels are described. Five of the seven patients had either an associated malignancy or severe interstitial lung disease. The one-year survival of the six patients followed for that length of time was 33 percent. A lack of creatine kinase elevation in patients with dermatomyositis is a poor prognostic sign.

Polymyositis and dermatomyositis are inflammatory myopathies that commonly are associated with elevation of serum muscle enzyme levels. Creatine kinase is the muscle enzyme most widely used to diagnose polymyositis/dermatomyositis and to follow response to therapy [1-3]. Although most patients with polymyositis/dermatomyositis present with increased creatine kinase levels, reported series include some patients with normal creatine kinase levels at presentation [1,2]. The course of this set of patients has not been addressed in the literature. After reviewing the records of all adults with polymyositis/dermatomyositis seen at the University of Michigan since 1979, it became apparent that a normal creatine kinase level at the time of diagnosis was associated with a poor prognosis. Of 38 patients reviewed, seven were found with normal creatine kinase levels and are the subject of this report (Table I).

CASE REPORTS

Patient 1. A 69-year-old white woman was admitted to the University of Michigan Medical Center in October 1980, because of a rash of six months' duration and increasing proximal muscle weakness of two months' duration. On admission she had erythema with telangiectasias over her face, posterior neck, anterior chest, and dorsum of hands. Proximal muscle strength was 3/5 with normal distal muscle strength. Laboratory data included creatine kinase 71 IU/liter (normal 30 to 225 IU/liter), aldolase 12 units/ml (normal 3 to 11 units/ml), serum glutamic oxaloacetic transaminase 25 IU/liter (normal 2 to 35 IU/liter), lactic dehydrogenase 267 IU/liter (normal 60 to 200 IU/liter), rheumatoid factor 1:320, and no demonstrable antinuclear antibody. Electromyographic results were interpreted as an inflammatory myopathy. Biopsy of the right deltoid muscle showed a perivascular lymphocytic infiltrate and degenerative fibers. An evaluation for possible malignancy included chest radiography, barium enema, upper gastrointestinal series, intravenous pyelography, and mammography, all of which showed negative results. Therapy with prednisone 60 mg every day was begun with improvement in strength. In January 1981, axillary and supraclavicular adenopathy developed. Biopsy revealed metastatic adenocarcinoma of unknown primary. She died three months later.

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TABLE I Patients with Dermatomyositis and Normal Creatine Kinase Levels

Patient	Age (years), Sex	Creatine Kinase at Diagnosis (IU/liter)	Associated Findings	Outcome
1	69, F	71	Adenocarcinoma, unknown primary	Died, six months after diagnosis
2	61, M	59	Small cell carcinoma of lung	Died, 12 months after diagnosis
3	42, F	170	Interstitial lung disease	Died, 10 months after diagnosis
4	55, F	34		Alive, 24 months after diagnosis
5	67, F	176		Alive, 19 months after diagnosis
6	55, F	38	Interstitial lung disease	Died, two months after diagnosis
7	76, M	177	Transitional cell carcinoma of prostate	Alive, five months after diagnosis

Patient 2. A 61-year-old white man was admitted in January 1982, with a six-month history of a pruritic maculopapular rash and a four-month history of proximal muscle weakness. Physical examination showed a diffuse erythematous rash over the arms, trunk, and legs with Gottron's papules over the metacarpophalangeal joints. Muscle strength was 3 to 4/5 proximally and 5/5 distally. Laboratory data included creatine kinase 59 IU/liter, aldolase 11 units/ml, serum glutamic oxaloacetic transaminase 12 IU/liter, lactic dehydrogenase 271 IU/liter, and Westergren sedimentation rate 95 mm per hour. Electromyography showed an inflammatory proximal myopathy. Biopsy of the right deltoid muscle showed degeneration, regeneration, phagocytosis, necrosis, and a slight perivascular lymphocytic infiltrate. An evaluation for possible malignancy included chest radiography, barium enema, upper gastrointestinal series, intravenous pyelography, and abdominal ultrasound, all of which showed normal results. He was treated with prednisone 60 mg every day and returned to normal strength in two months. In September 1982, he was found to have small cell carcinoma of the lung, and died four months later despite chemotherapy.

Patient 3. A 42-year-old white woman was admitted in May 1982, with a three-month history of an erythematous rash and a two-month history of proximal muscle weakness and dyspnea on exertion. Examination showed Gottron's papules on her fingers and a heliotrope rash. The lungs were clear. Proximal muscles had 4/5 strength and distal muscles were 5/5. Her creatine kinase level was 170 IU/liter, serum glutamic oxaloacetic transaminase level 65 IU/liter, lactic dehydrogenase level 348 IU/liter, aldolase level 14 units/ml, and rheumatoid factor 1:160; antinuclear antibody was not demonstrable and total hemolytic complement was normal. Chest radiography showed a reticular nodular pattern. Electromyography was diagnostic for an inflammatory myopathy. Muscle biopsy of the left deltoid showed a few fibers with internal nuclei, but otherwise demonstrated normal findings. Gallium-67 scanning showed intrapulmonary uptake consistent with active alveolitis. Transbronchial biopsy revealed focal interstitial and intra-alveolar fibrosis and pneumatocyte hypertrophy. The patient began to receive prednisone 30 mg twice a day. Over the next three months, her strength improved but the dyspnea and rash did not. In October 1982, her condition deteriorated with proximal muscle strength again 4/5, and chest radiography showed increasing infiltrates. She was treated with azathioprine and later cyclophosphamide with

transient improvement in her muscle strength. She died in March 1983 of progressive respiratory insufficiency and sepsis.

Patient 4. A 55-year-old black woman was admitted in November 1982, with a three-month history of arthralgias, rash, proximal muscle weakness, and weight loss. On examination she had a maculopapular rash over the dorsum of her hands, on her neck, and shoulders. Proximal muscles were 4/5 with normal distal muscle strength. Laboratory data included creatine kinase 34 IU/liter, aldolase 11 units/ml, serum glutamic oxaloacetic transaminase 107 IU/liter, Westergren sedimentation rate 115 mm per hour, rheumatoid factor 1:640, no demonstrable antinuclear antibody, and normal total hemolytic complement, C3, and C4. Electromyography showed evidence of a moderate to severe inflammatory myopathy. Muscle biopsy of the right thigh showed necrosis, phagocytosis, regenerating fibers, and perivascular inflammatory infiltrates. Results of chest radiography, barium enema, upper gastrointestinal series, and mammography were negative. Therapy was begun with prednisone 40 mg twice a day with resolution of muscle weakness. She is currently taking prednisone 5 mg every day.

Patient 5. A 67-year-old white woman was admitted in February 1983, with a two-year history of proximal muscle weakness, Raynaud's phenomenon, and arthritis of the wrists, hands, and shoulders. On examination she was found to have a faint heliotrope rash, Gottron's papules on the distal interphalangeal joints, and an erythematous macular rash on the trunk and extensor surface of the arms. Proximal muscle strength was 4/5 with normal distal muscle strength. Laboratory data included creatine kinase 176 IU/liter, serum glutamic oxaloacetic transaminase 39 IU/liter, lactic dehydrogenase 361 IU/liter, and no demonstrable rheumatoid factor or antinuclear antibody. Electromyography showed a proximal myopathy. Biopsy of the right quadriceps muscle showed degeneration, regeneration, phagocytosis, necrosis, and areas of dense perivascular and interstitial inflammatory infiltrates with monocytes, lymphocytes, and plasma cells. An evaluation for possible malignancy was unrevealing with normal results of barium enema, upper gastrointestinal series, and liver/spleen scanning. Therapy was begun with prednisone 20 mg twice a day. By July 1983, her muscle strength had returned to normal and the rash had resolved. She is currently taking prednisone 5 mg every day with normal muscle strength.

Patient 6. A 55-year-old white woman was admitted in

March 1984, for dyspnea and proximal muscle weakness. In September 1983, arthralgias of her fingers, wrists, and knees began to develop. An erythematous rash on her forehead developed the following month. In January 1984, she noticed myalgias of shoulder and thigh muscles and had difficulty climbing stairs. Creatine kinase level was measured by her personal physician and was 156 IU/liter (normal range 50 to 250). Treatment with prednisone 30 mg every day was begun and was tapered over the next several weeks to 15 mg every day. In February 1984, a nonproductive cough and dyspnea on exertion developed and she was referred to the University of Michigan. Results of physical examination were significant for erythema over the metacarpophalangeal and proximal interphalangeal joints and digital ulcerations in various stages of healing. Rales were present in the lower lung fields. The iliopsoas muscles had 4/5 strength with normal strength of other muscle groups. Laboratory data included creatine kinase 38 IU/liter, aldolase 7 units/ μ l, serum glutamic oxaloacetic transaminase 160 IU/liter, no demonstrable antinuclear antibody or cryoglobulins, and normal total hemolytic complement. Chest radiography showed a reticulonodular infiltrate throughout most of the left lung and the lower half of the right lung. Electromyography showed a severe inflammatory myopathy. The only abnormality seen on muscle biopsy was type II fiber atrophy. Transbronchial biopsy showed interstitial fibrosis. The patient was treated with pulse methylprednisolone therapy for three days and was discharged receiving prednisone 60 mg every day. At a follow-up visit three weeks later, she was noted to have increased iliopsoas weakness. She died at home in May 1984.

Patient 7. A 76-year-old white man was admitted in April 1984, with a five-month history of an erythematous rash and a two-month history of proximal arm and leg weakness. On examination he was seen to have erythema of the face and chest, Gottron's papules, and erythematous plaques on the knees and buttocks. Muscle strength was 4/5 proximally and 5/5 distally. An enlarged prostate with a nodule was found. Laboratory data included creatine kinase 177 IU/liter, aldolase 5 units/ml, serum glutamic oxaloacetic transaminase 31 IU/liter, lactic dehydrogenase 234 IU/liter, and acid phosphatase 1.24 IU/liter (normal 0 to 0.80 IU/liter). Results of electromyography were interpreted as a moderately severe inflammatory myopathy. Biopsy of the left biceps revealed only mild nonspecific changes with a few moth-eaten and granular fibers and two ragged red fibers. Further evaluation of the prostate found transitional cell carcinoma metastatic to inguinal lymph nodes. The patient declined therapy for the metastatic carcinoma. He was treated with prednisone 15 mg three times a day and currently takes 5 mg every day with improvement but not full strength.

COMMENTS

Dermatomyositis is classified as "definite" when the characteristic skin rash is present in addition to at least three of the following: (1) proximal muscle weakness, (2) elevation of levels of serum muscle enzymes, especially creatine kinase, (3) electromyographic findings of inflammatory myopathy, and (4) positive findings on muscle

biopsy. The diagnosis is "probable" when two criteria are met in addition to the rash [1]. Four of our patients met criteria for "definite dermatomyositis" and the other three met criteria for "probable dermatomyositis" before levels of serum enzymes were taken into account. If the elevations in levels of lactic dehydrogenase, serum glutamic oxaloacetic transaminase, and/or aldolase are considered as sufficient to satisfy the second criterion, all seven patients met criteria for "definite dermatomyositis."

Three patients had a malignancy associated with dermatomyositis and two others had severe interstitial lung disease in addition to skin and muscle involvement. Four of the seven patients died a mean of nine months from the onset of weakness (range four to 15 months), and a mean of seven months after diagnosis (range two to 12 months). A fifth patient has metastatic cancer and thus far has survived seven months from the onset of weakness and five months from diagnosis. The one-year survival for the six patients followed for at least that length of time was 33 percent. This survival is dramatically lower than the 75 to 90 percent one-year survival reported in two large series of polymyositis and dermatomyositis [2,4] and the 100 percent one-year survival of the remainder of the patients with polymyositis/dermatomyositis followed here.

The association between myositis and malignancy is controversial. The strongest association is that reported between malignancy and dermatomyositis. A recent review of the reported series of patients with polymyositis and dermatomyositis concluded that approximately one-fourth of patients with dermatomyositis also had a malignancy, but the two were concurrent in only one third of those cases [5]. In our series, three of the seven cases of dermatomyositis with normal creatine kinase levels were associated with malignancy. The cancer was apparent in only one of the patients when dermatomyositis was diagnosed. This association with malignancy is higher than would be expected from the literature. However, it is possible this finding is an artifact of our small sample size.

Interstitial lung disease is increasingly being recognized as a feature of polymyositis/dermatomyositis. Such pulmonary involvement has been detected radiographically in 5 to 10 percent of patients in some series [6-8]. Of the 65 cases reported in the English literature, about half have been associated with polymyositis and half with dermatomyositis [8]. The finding that two of seven patients with dermatomyositis and normal creatine kinase levels had severe, progressive interstitial lung disease strongly suggests that patients with normal creatine kinase levels are at risk for pulmonary manifestations of dermatomyositis.

Conditions that cause an abnormally low serum creatine kinase level, or that prevent an expected rise in creatine kinase level, are not well defined. Wei et al [9] found a lower mean creatine kinase level in patients with connective tissue disease than in a control population, but the mechanism for this observation was not reported. Low creatine kinase level has been found in some patients

with liver diseases, including carcinoma metastatic to the liver [10], alcoholic liver disease [11], and viral hepatitis [12]. It has also been reported in patients being treated with steroids [13] and cancer chemotherapy [14]. We do not have a unifying explanation for the lack of creatine kinase elevation in the seven cases reported here. None of the patients were cachectic or immobile. Three of the patients (Patients 3, 4, and 5) had follow-up creatine kinase levels below the normal range while under treatment, which might suggest the lower average creatine kinase level found in patients with connective tissue disease combined with myositis resulted in normal creatine

kinase levels in some patients. These three patients were treated with steroids, which is another possible explanation for the subnormal creatine kinase level, as just noted [13], although the other four patients also received steroids.

These seven cases demonstrate the poor outcome of dermatomyositis without creatine kinase elevation. A normal creatine kinase level should not stop physicians from pursuing a diagnosis of inflammatory myopathy when there is strong clinical suspicion. If the diagnosis is ultimately made using other criteria, close follow-up for malignancy and interstitial lung disease is indicated.

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