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**Case Reports**

**D-Penicillamine-Induced Polymyositis Occurring in Patients with Rheumatoid Arthritis: A Report of Two Cases and Demonstration of a Positive Lymphocyte Stimulation Test to D-Penicillamine**

Takayuki Matsumura, MD,* Takamichi Yuhara, MD,* Kazuhide Yamane, MD,* Ichiro Kono, MD,* Teizo Kabashima, MD,* and Heihachiro Kashiwagi, MD†

Two patients with erosive, seropositive rheumatoid arthritis developed polymyositis during treatment with D-penicillamine. In both patients the HLA tissue typing revealed the presence of DR4. The myopathy improved promptly after withdrawal of D-penicillamine and institution of prednisolone therapy. In one patient, hypersensitivity to D-penicillamine was demonstrated by a lymphocyte stimulation test. This is the first case of D-penicillamine-induced polymyositis in which T-cell proliferative response to D-penicillamine was demonstrated in vitro. (Henry Ford Hosp Med J 1986;34:123-6)

D-penicillamine (D-PC) has been a useful drug in the treatment of rheumatoid arthritis, but adverse reactions are reported to occur in about half of the patients during treatment with D-PC (1-3). Certain autoimmune diseases, such as systemic lupus erythematosus, myasthenia gravis, and pemphigoides, have been reported as complications of D-PC therapy. Since Schraeder et al (4) first reported D-PC-induced polymyositis in a patient with Wilson’s disease, reports of this unusual complication have sporadically appeared in the literature, although evidence of hypersensitivity to D-PC has never been proved in vitro. This report describes two cases of D-PC-induced polymyositis; in one case, a lymphocyte stimulation test demonstrated the presence of sensitized T-cells to D-PC.

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**Case Reports**

**Case 1**

A 45-year-old woman developed an erosive, seropositive rheumatoid arthritis in 1970. As her response to nonsteroidal antiinflammatory drugs was unsatisfactory, chrysotherapy was started in October 1981, but was discontinued in January 1982 because of skin rash. In July 1982, 100 mg/day of D-PC was instituted; one month later this dosage was increased to 200 mg/day (Fig 1). The patient’s arthritis improved gradually, but the dosage of D-PC was reduced to 100 mg/day because of the development of skin rash. After 14 months’ therapy of D-PC, the patient complained of rapidly progressive weakness in proximal muscles, dysphagia, and dyspnea. Drug-induced polymyositis was considered, and D-PC was withdrawn. She was admitted to our hospital on October 6, 1983. The patient denied penicillin allergy, and her past history and family history were noncontributory.

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![Fig 1: Clinical course of case 1 demonstrating the relationships between drug administration, muscle weakness, and serum concentrations of muscle enzymes. CPK = creatinine phosphokinase, LDH = lactate dehydrogenase, SGOT = glutamate oxaloacetate transaminase, D-PC = D-penicillamine, and PSL = prednisolone.](image-url)
On admission, the patient had no skin rash or muscle tenderness. There were digital deformities due to rheumatoid arthritis, and moderate weakness existed in the upper and lower limb girdle muscles and neck flexor muscles. No neurological abnormality was found.

Laboratory investigation revealed the following findings. Complete blood count was normal. Serum levels of myogenic enzymes were markedly elevated with creatinine phosphokinase (CPK) level of 7,749 IU/L (normal < 30 IUL); lactate dehydrogenase (LDH) 2,748 IU/L (normal < 400 IU/L); glutamate oxaloacetate transaminase (SGOT) 442 IU/L (normal < 40 IU/L); glutamic pyruvic transaminase (SGPT) 295 IU/L (normal < 35 IU/L); and aldolase (ALD) 204 IU/L (normal < 10 IU/L). ESR was 13 mm/hr, and CRP was 1+. Rheumatoid factor was positive at 1:1,640 dilution. A test for antinuclear antibody was positive at 1:1,640 dilution (diffuse and speckled pattern). Anti-DNA antibody, anti-RNP antibody, anti-SS-B antibody, and LE cell were all negative. Serum levels of C3 and C4 as well as CH50 activity were within the normal range. Serum antibody titers for influenza A and B and Coxsackie A and B viruses were negative. Thyroid function was within the normal range.

Electromyography of the deltoid, brachial biceps, and gastrocnemius muscles demonstrated changes compatible with myositis (low amplitude, short duration, and polyphasic potentials). Histological examination of the right quadriceps muscle biopsy showed perivascular inflammatory cell infiltration compatible with myositis. There was no evidence of muscle cell damage. The HLA tissue typing revealed A9, Bw6, Bw40, Bw6, and DR4.

Case 2

A 50-year-old woman developed an erosive, seropositive rheumatoid arthritis and Raynaud phenomenon in January 1978. She had been given two courses of chrysotherapy, each of which had to be withdrawn because of skin rash. D-PC was instituted at an initial dose of 100 mg/day of prednisolone was added to her medication regimen. In November 1979, her arthritis exacerbated again, and 5 mg/day of prednisolone was added to her medication regimen. In September 1983, the patient noticed difficulty in climbing stairs and lifting heavy objects. Myogenic enzymes examined at this time were found to be elevated. The patient denied penicillin allergy, and her past and family histories were noncontributory.

On admission, the patient had no skin rash or muscle tenderness. Muscle weakness was present in the proximal muscles of the upper and lower extremities and neck flexor muscles. Results of other physical examinations were normal. Laboratory investigations revealed the following findings. Complete blood count was normal. Urinalysis was normal. Serum levels of myogenic enzymes were elevated with CPK 3,108 IU/L; LDH 1,941 IU/L; SGOT 183 IU/L; SGPT 157 IU/L; and ALD 125 IU/L. ESR was 6 mm/hr. CRP was negative. Rheumatoid factor was positive at 1:160 dilution. Antinuclear antibody was positive at 1:80 dilution (speckled pattern). Anti-RNP antibody, anti-SS-B antibody, and LE cell were negative. Serum level of C3 was 43 mg/dL (normal 55 to 120 mg/dL), that of C4 was 15 mg/dL (normal 20 to 50 mg/dL), and CH50 was 30.1 U/mL (normal 30 to 40 U/mL).

Electromyography of the sternocleidomastoid, trapezius, and deltoid muscles demonstrated myopathic changes with low amplitude, short duration, and polyphasic potentials. Histological examination of the left deltoid muscle showed myogenic degeneration with a slight inflammatory cell infiltration. There was no evidence of muscle cell damage. The HLA tissue typing revealed Aw31, B40, Bw6, and DR4. D-PC-induced myositis was highly suspected, and an initial dose of 60 mg/day of prednisolone was started. Myogenic enzymes quickly decreased after the therapy and normalized within three months. Muscle weakness improved within six months. The patient remained in remission throughout the following two years.

Case 2

A 50-year-old woman developed an erosive, seropositive rheumatoid arthritis and Raynaud phenomenon in January 1978. She had been given two courses of chrysotherapy, each of which had to be withdrawn because of skin rash. D-PC was instituted at an initial dose of 100 mg/day of prednisolone was added to her medication regimen. In November 1979, her arthritis exacerbated again, and 5 mg/day of prednisolone was added to her medication regimen. In September 1983, the patient noticed difficulty in climbing stairs and lifting heavy objects. Myogenic enzymes examined at this time were found to be elevated. The patient denied penicillin allergy, and her past and family histories were noncontributory.

On admission, the patient had no skin rash or muscle tenderness. Muscle weakness was present in the proximal muscles of the upper and lower extremities and neck flexor muscles. Results of other physical examinations were normal. Laboratory investigations revealed the following findings. Complete blood count was normal. Urinalysis was normal. Serum levels of myogenic enzymes were elevated with CPK 3,108 IU/L; LDH 1,941 IU/L; SGOT 183 IU/L; SGPT 157 IU/L; and ALD 125 IU/L. ESR was 6 mm/hr. CRP was negative. Rheumatoid factor was positive at 1:160 dilution. Antinuclear antibody was positive at 1:80 dilution (speckled pattern). Anti-RNP antibody, anti-SS-B antibody, and LE cell were negative. Serum level of C3 was 43 mg/dL (normal 55 to 120 mg/dL), that of C4 was 15 mg/dL (normal 20 to 50 mg/dL), and CH50 was 30.1 U/mL (normal 30 to 40 U/mL).

Electromyography of the sternocleidomastoid, trapezius, and deltoid muscles demonstrated myopathic changes with low amplitude, short duration, and polyphasic potentials. Histological examination of the left deltoid muscle showed myogenic degeneration with a slight inflammatory cell infiltration. There was no evidence of muscle cell damage. The HLA tissue typing revealed Aw31, B40, Bw6, and DR4. D-PC-induced myositis was highly suspected, and an initial dose of 60 mg/day of prednisolone was instituted. Muscle enzymes gradually improved and were normalized within nine months. Muscle weakness improved within four months. The patient remained in remission during the following two years.

Lymphocyte Stimulation Test

Lymphocyte stimulation test (LST) was performed to investigate whether lymphocytes of the two patients were immunologically sensitized by D-PC. The method of LST was as follows: 10 mL of blood was withdrawn from the patients, and mononuclear cells were separated by Ficoll-Hypaque density gradient centrifugation. Mononuclear cells were suspended in RPMI 1640 medium with 10% patient’s plasma at the density of 1 X 10^6 per mL. Aliquots of mononuclear cells were cultured with various concentrations of D-PC (0, 1, 2.5, 5, 10, 20, 50, and 100 mg/mL) for seven days at 37°C in a 5% CO2 incubator in 96 wells microtiter plates. Twenty-four hours prior to harvest, 0.5 μCi of 3H-thymidine (Amersham, UK, sp. act. 5 Ci/mmol) was added to each well. The cultured cells were harvested on glass wool filters by a multiple-harvesting system. The radioactivities of the filters were counted by a liquid scintillation counter. The results were expressed as counts per minute (cpm) of the mean of triplicate cultures. Stimulation index (SI) was calculated as follows:

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SI (%) = \frac{cpm \text{ of cultures with } D-PC}{cpm \text{ of cultures without } D-PC} \times 100
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The data of a representative experiment for case 1 are shown in the Table. All experiments were performed in triplicate, with the variability among triplicate cultures within 5%. The background counts were 295 cpm. SI was greater than 200% at the D-PC concentrations (μg/mL) of 1.25, 2.5, and 5. A similar value of SI for case 1 was observed one week after D-PC treatment.

As the SI values were 100 ± 2% (mean ± SE), the concentration of D-PC in case 1 was considered to be 0.01% (SI 110%).

Both of the patients were repeatedly treated with D-PC. In January 1979, the patient had a 10-month episode of preexisting myositis of the left deltoid muscle, followed by D-PC-induced polymyositis. The other patient was treated with the same regime. Both of the patients complained of weakness in the left deltoid muscles. The left deltoid muscle showed both myositis and myopathy. The left deltoid muscle also showed an inflammatory cell infiltration.
of SI for case 1 was obtained from two experiments performed one week apart.

As the SI of mononuclear cells from normals (n = 5) was 100% ± 20% (mean ± SI), the SI greater than 200% with any concentration of D-PC was considered to be positive. The SI of case 1 was positive (SI 312%) and that of case 2 was negative (SI 110%).

Discussion

Both of our patients had erosive, seropositive rheumatoid arthritis with histories of skin rash to chrysotherapy. Polymyositis, developed during D-PC treatments, fulfilled the criteria outlined by Bohan and Peter (5). Rheumatoid arthritis and polymyositis rarely coexisted, but it is not impossible that D-PC exacerbated the preexisting polymyositis. However, normal serum levels of muscle enzymes and the absence of muscle weakness prior to the episode make this assumption unlikely. In our patients, the myopathy promptly improved after cessation of D-PC and responded to steroid therapy. During two years of follow-up, both patients remained in remission. The foregoing evidence indicates that polymyositis in our patients was D-PC induced.

According to the available literature, D-PC-induced myositis was reported in one patient with Wilson's disease (4), one with juvenile chronic rheumatoid arthritis (6), five with progressive systemic sclerosis (7,8), and 18 with rheumatoid arthritis (9-24). A summary of the 18 patients with rheumatoid arthritis was as follows: male to female ratio was 5:13; the duration of rheumatoid arthritis prior to the complication spanned from eight months to 12 years, with a mean of 4.2 years; the age of onset of D-PC-induced myositis ranged from 39 to 69 years, with a mean age of 51.7 years; daily doses of D-PC were 250 to 1,200 mg/day; and the duration of D-PC treatment prior to the complication ranged from one to 72 months, with 80% of the cases occurring within one year of the D-PC therapy. The ratio of polymyositis versus dermatomyositis was 11:7. Clinical symptoms, electromyographic findings, and the results of histological examinations were similar to idiopathic myositis. Serological studies demonstrated rheumatoid factor in all but one patient. Antinuclear antibody was positive in ten of the 12 patients whose results were described. Reduced levels of complement components were observed in four patients. Nine patients were treated with prednisolone in doses ranging from 25 to 80 mg. Five patients either received no therapy or low doses of prednisolone after the withdrawal of D-PC. The outcome of these patients was as follows: two patients died from cardiac complications (19,23), and 13 patients improved within about six months. Except for the two fatalities, the patients showed no recurrence of the disease clinically or in laboratory findings. The foregoing data suggest that D-PC-induced polymyositis is indistinguishable from idiopathic polymyositis by clinical or laboratory findings at the onset. The clues to D-PC-induced myositis are the temporal relationship between D-PC treatment and the development of myositis and the clinical suspicion of the possible causative relationship. LST in patients with allergic reactions to a variety of drugs has been investigated (25,26), and the test has been proved useful in evaluating adverse drug reactions. No abnormal reactions have yet been reported in LST for D-PC in patients who developed polymyositis during the drug treatment. One of our patients demonstrated a positive result in LST for D-PC, which suggests that hypersensitivity to D-PC might be operative in the pathogenesis of polymyositis.

The mechanism of D-PC-induced myositis remains obscure. Ostensen et al (14) assumed that a hapten-like linkage of D-PC to skeletal muscle might make the muscle immunogenic, thus providing the basis for an autoimmune disease. However, Peterson et al (12) suggested that D-PC might lead to an atrogeneric immune complex disease with deposits of immune complexes in the skin. Hypocomplementemia, reported previously and demonstrated in one of our patients, is not inconsistent with the immune complex hypothesis in D-PC-induced myositis.

Recently, it has been emphasized that major histocompatibility complex molecules, including HLA-DR antigens, may regulate immune responses of individuals to various antigens. There were several reports describing HLA-DR antigens, which is present at approximately a 40% level among the Japanese population (29) and is seen with high frequency in those with rheumatoid arthritis (30). The number is too small to conclude the association between HLA and D-PC-induced myositis.

References