Polymyositis complicating D-penicillamine treatment

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Summary: Although there is good evidence that D-penicillamine can induce polymyositis, the exact pathogenic mechanism remains unclear. We report two patients with psoriatic arthritis and primary biliary cirrhosis respectively, who developed polymyositis while receiving D-penicillamine treatment for their primary diseases. Whether D-penicillamine treatment was the sole cause of polymyositis or acted as a trigger for the development of a secondary autoimmune disease is discussed.

Introduction

There is good evidence that D-penicillamine (DP) can induce a polymyositis-like syndrome.^{1,2} The frequency of this complication has varied between 0.2–1.2% in previous reports^{3–5} although the exact pathogenic mechanism remains unclear.

In this paper, we report two patients, one with psoriatic arthritis and one with primary biliary cirrhosis, who developed polymyositis while receiving DP treatment for their primary diseases. The diagnosis of polymyositis was assigned according to Bohan and Peter's criteria.⁶

Case reports

Case 1

A 41 year old woman with a 10-year history of psoriasis and seronegative, erosive arthritis had been receiving DP (500 mg/day) for 5 years when her arthritis flared in August 1986. She was then put on sulphasalazine and her DP was reduced to 250 mg/day. In April 1987 she presented with severe symmetrical muscle weakness having lost 6.5 kg over the 2 previous weeks. Her serum creatine kinase (CK) was 14,000 IU/l (normal < 250 IU/l). Autoantibodies including antinuclear antibody (ANA), anti-ds DNA, antibodies against extractable nuclear antigens (ENA), anti-Jo-1 and anti-acetylcholine receptor antibodies (anti-AChR) were negative. Electromyography showed evidence of a very severe proximal and severe distal

active inflammatory myopathy with the presence of polyphasic potentials and fibrillation. A muscle biopsy disclosed necrosis, vacuolar degeneration and regeneration of muscle fibres with some fibrosis, and a mild lymphocytic infiltrate which on immunohistochemical staining was due to the presence of cytotoxic/suppressor T cells. No immunoglobulin or complement deposition was seen in vessel walls. This was consistent with the diagnosis of polymyositis. DP was stopped and she received 3 intravenous pulses of methylprednisolone (1 g each) given on alternate days followed by oral prednisolone (80 mg/day) and azathioprine (100 mg/day). She improved clinically over the next 6 weeks but her CK levels remained persistently elevated at 3950 IU/l. Azathioprine was increased to 150 mg/day and the dose of prednisolone was gradually reduced to less than 10 mg/day. In March 1989, 2 years after the cessation of DP, CK levels returned to normal values. There has been no recurrence of polymyositis since then.

Case 2

A 56 year old woman with primary biliary cirrhosis of 5 years duration had been taking DP (250 mg/day) for 5 years when she presented to another hospital with generalized myalgia and proximal muscle weakness in February 1981. Her CK was then reported to be 141 IU/l (N < 50 IU/l). Anti-AChR were found to be positive. A muscle biopsy showed an inflammatory myopathy with increased variability of muscle fibre size with scattered atrophic fibres. A number of these were basophilic indicating regeneration. Sparse inflammatory infiltrates were present in the endomysial connective tissues and were occasionally seen in relation to blood vessels. Electromyography showed minor

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myopathic changes. DP was stopped and she was put on azathioprine (150 mg/day) and prednisolone (50 mg on alternate days) for one year. These failed to improve her symptoms and her CK remained elevated at 681 IU/l ($N < 200$ IU/l), but anti-AChR became negative. These were attributed to DP because there was no clinical evidence for myasthenia gravis. Repeat electromyography showed no decrement in the evoked response after maximum voluntary effort.

She had been taking DP intermittently from 1982 to 1988 when she was referred to our hospital in 1988 with a marked exacerbation of her proximal muscle weakness. D-Penicillamine had been discontinued for 6 weeks and ANA, anti-dsDNA, antibodies against ENA, anti-AChR, anti-Scl and anti-Jo-1 antibodies and rheumatoid factor were negative. Electromyography showed profuse fibrillation potentials and an excess of small polyphasic potentials on volition. The appearances were those of a chronic polymyositis with evidence of continuing activity. A formal Lambert test for a defect of neuromuscular transmission was performed which showed no decrement at rest or after 10 and 60 seconds of maximal exercise. Despite treatment with 4 intravenous pulses of cyclophosphamide she did not show any clinical improvement; her CK was 270 IU/l. She has subsequently been lost to follow-up.

Discussion

Several cases of polymyositis have been closely associated with DP treatment.^{1-5,7-9} It has been suggested that DP has a unique ability to induce autoantibody formation¹⁰ and DP treatment has also been implicated as the cause of several other autoimmune disorders such as dermatomyositis,¹¹ systemic lupus erythematosus,^{12,13} Sjögren's syndrome,¹⁴ Goodpasture's syndrome,¹⁵ myasthenia gravis¹⁶ and pemphigus.¹⁷ There is also an interesting case report concerning a patient with rheumatoid arthritis who developed systemic lupus erythematosus and myasthenia gravis and then polymyositis sequentially during DP treatment.¹⁸

The development of polymyositis associated with DP appears to be an idiosyncratic reaction that does not have any relationship to dose or duration of administration. Some patients reported developed polymyositis after 4 weeks or less, whereas other patients became symptomatic after 5 years or more of DP therapy.^{4,8,9} In our patients, the

duration and the cumulative dose of therapy prior to the development of polymyositis were 5 years and 6 years and 450 g and 966 g respectively. Interestingly, case 1 developed polymyositis 8 months after her DP dose had been halved.

The clinical, laboratory and pathological features of our patients were indistinguishable from those seen in idiopathic polymyositis.^{6,19} There were no skin changes. Contrary to a study which suggests a rapid recovery after DP discontinuation and a more benign course for DP-induced polymyositis,⁵ it took 2 years in Case 1 to have a complete clinical and laboratory improvement despite therapy with high dose steroids and azathioprine. Case 2 did not show any improvement whatsoever despite adequate immunosuppressive therapy.

Although the exact aetiopathogenesis of DP-induced polymyositis is not known, it is thought that some effects of DP on the humoral immunological system might play some role.^{10,20} Interestingly, Case 2 was noted to have a transient anti-AChR positivity following the development of polymyositis. Development of such anti-AChR without evidence of myasthenia gravis has been previously reported to occur during treatment with DP.²¹

Since DP-induced polymyositis can emerge at any time during the course of therapy and with any dose, it is prudent to monitor patients receiving DP closely. Should polymyositis develop, it is generally advisable to discontinue treatment. In view of the risk of significant morbidity and mortality,⁹ specific treatment should not be unduly delayed. Rechallenge with DP is generally discouraged as there have been reports of exacerbation of polymyositis with a second challenge.^{4,7} However, Carroll *et al.*⁵ suggest that, in patients with rheumatoid arthritis who have developed DP-induced polymyositis, it may be possible to continue or only temporarily interrupt treatment with DP if corticosteroids are administered.

Whether DP treatment was the sole cause of polymyositis or acted as a 'trigger' for the development of a secondary or an 'overlap' type of autoimmune disease in patients who already have had a primary autoimmune disorder remains unknown. It may be that some patients are genetically predisposed to developing DP-induced polymyositis and indeed it has been reported that HLA-B18, B35 and DR4 are associated with this condition and that this differs immunogenetically from idiopathic inflammatory myopathy.⁵

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