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CASE REPORT

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Congestive heart failure and axonal polyneuropathy induced by alfacalcidol in a patient with systemic lupus erythematosus

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Abstract We describe the case of a 29-year-old woman with systemic lupus erythematosus (SLE), who developed congestive heart failure and severe axonal polyneuropathy after 9 months of treatment with alfacalcidol for the prevention of corticosteroid-induced osteoporosis. There was no evidence for the exacerbation of SLE. Moreover, both congestive heart failure and axonal polyneuropathy improved after discontinuation of the alfacalcidol without increasing the dose of corticosteroid. Since alfacalcidol is commonly used in the prevention of corticosteroid-induced osteoporosis, rheumatologists should be aware of the presence of this life-threatening adverse effect.

Key words Corticosteroid · Osteoporosis · Side effects · Systemic lupus erythematosus (SLE) · Vitamin D

Introduction

Patients with systemic lupus erythematosus (SLE) or other rheumatic diseases are at risk of osteoporosis through the inflammatory disease process as well as from treatment with corticosteroids.[1–3] Treatment with alfacalcidol (1α-OH-vitamin D_3) has been shown to be effective in preventing corticosteroid-induced osteoporosis,[4,5] and is therefore frequently used. Most of the toxic effects of alfacalcidol, including appetite loss, nausea, constipation, liver dysfunction, renal dysfunction, ectopic calcification, and hypercalcemia, are not serious and disappear shortly after the discontinuation of alfacalcidol. Thus, no serious side-effects of alfacaldcidol have been described.

Here, we describe a patient with SLE who developed congestive heart failure and axonal neuropathy after 9 months of treatment with alfacalcidol. These manifestations improved and disappeared after the discontinuation of alfacalcidol without increasing the doses of corticosteroid, indicating that they were induced by the alfacalcidol.

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Case report

A 29-year-old woman was referrend to our hospital in April 2000 for evaluation of persistent low-grade fever. The presence of photosensitivity and the results of leukocytopenia with lymphocytopenia, proteinuria (more than 0.5 g/day), positive antinuclear antibody (ANA), and elevated anti-DNA antibody confirmed the diagnosis of SLE. Treatment with oral prednisolone (30 mg/day) was started, along with alfacalcidol (0.5 μg/day) to prevent osteoporosis. With this treatment, proteinuria as well as leukocytopenia improved, along with a decrease in ANA titers and anti-DNA antibody levels, and the dose of prednisolone was gradually decreased.

In January 2001, when the patient was taking 11 mg/day prednisolone, she presented with painful swelling in her bilateral lower extremities, followed by the development of numbness and muscle weakness in her bilateral upper and lower extremities. In early February 2001, she further complained of shortness of breath with edema in her bilateral legs. There was no facial edema or jugular vein dilatation. Chest auscultation revealed no pericardial friction sound. The blood tests on February 17 showed an elevation of creatin kinase (452 U/ml), but no abnormalities suggestive of an exacerbation of SLE. Serum C-reactive protein was negative. However, a chest X-ray showed right pleural effusion with cardiac enlargement (Fig. 1A). Alfacalcidol was discontinued at this time, but the dose of prednisolone was not changed. No other drugs had been given to the patient. After the discontinuation of alfacalcidol, the leg edema as well as the pleural effusion and cardiac enlargement improved (Fig. 1B, Fig. 2). However, the numbness in the extremities and the muscle weakness still increased, and resulted in gait disturbance. She was therefore admitted to

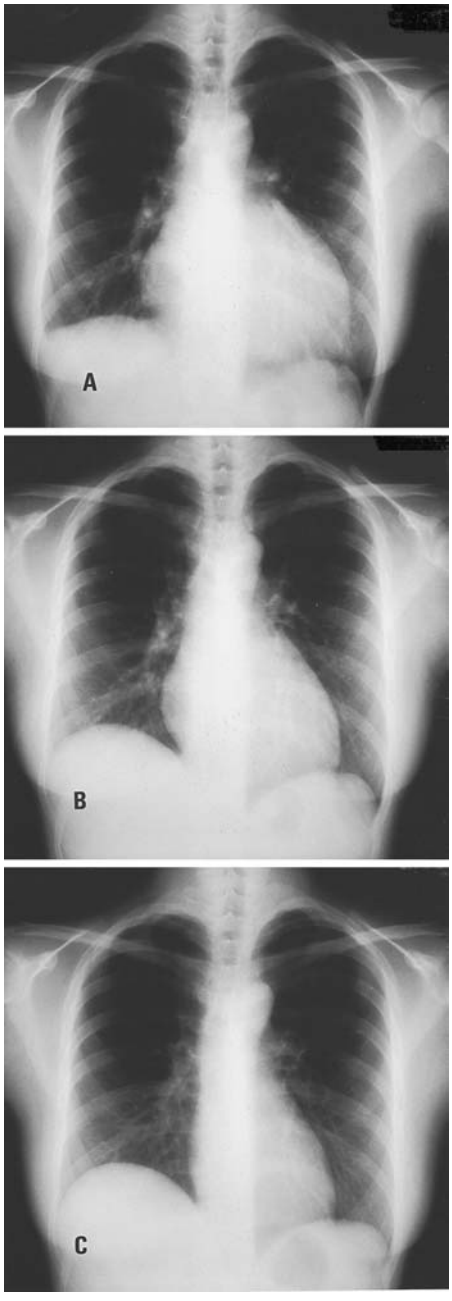


Fig. 1. Chest X-ray of the patient. **A** Showing right pleural effusion with cardiac enlargement (February 17, 2001). **B** Showing an improvement in cardiac enlargement and the disappearance of right pleural effusion (March 13, 2001). **C** Showing no abnormalities (April 5, 2001)

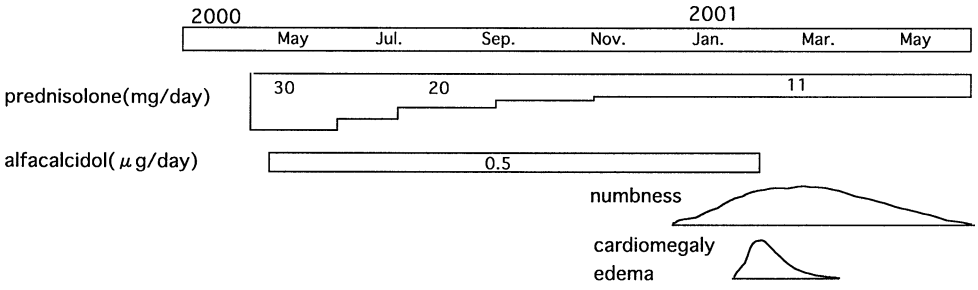
the Department of Neurology in our hospital on March 13, 2001.

On admission, her temperature was 36.5°C and her blood pressure 140/80 mmHg, with a pulse rate of 84 beats/min. A physical examination of the chest and abdomen revealed no abnormalities. Neurological examinations disclosed diffuse hyporeflexia with a disappearance of most tendon reflexes in the bilateral upper and lower extremities, the presence of hypesthesia and paresthesia in the bilateral upper and lower extremities (distal dominant), and muscle weakness, especially in the bilateral lower extremities. Laboratory studies showed mild elevation of creatin kinase (222 IU), aldorase (8.6 IU), uric acid (6.2 mg/dl), and lymphocytopenia (320/mm^3), and normal liver and renal functions. Westergren erythrocyte sedimentation rate was 5 mm/h. Serum C-reactive protein was negative. ANA was positive at a titer of 1:40 with a homogeneous and speckled patterns. Total hemolytic complement (CH50) was 35.0 U/ml (reference interval 29.3–43.9 U/ml). Anti-DNA was 10.5 U/ml (reference interval <20.0 U/ml), and anti-Sm and anti-RNP were <5.0 and <7.0, respectively. Both anticardiolipin/β_2 glycoprotein I and anticardiolipin (IgG) were negative. Antiganglioside antibody was negative. Immune complex determined by C1q binding assay was 2.5 μgEq/ml (reference interval <3.0 μgEq/ml). A chest X-ray on March 13 showed an improvement of cardiac enlargement and the disappearance of the right pleural effusion (Fig. 1B). An electrocardiogram on March 13 showed negative T in lead I and aV_L, but no abnormalities suggestive of pericarditis or myocarditis. Echo cardiography also showed no abnormalities. A neurophysiological examination revealed normal motor condition velocity, with a decrease in the amplitude of the M-wave in the right radial and tibial nerves, and silent activity in the left sural nerve, supporting the diagnosis of axonal neuropathy. Physical and laboratory examinations provided no evidence for an exacerbation of SLE. Therefore, the patient was treated with an empirical rehabilitation program only. She gradually recovered from the neurological impairment without any additional treatment after admission. On April 5, 2001, a chest X-ray was almost normal (Fig. 1C), and negative T waves in lead I and aV_L were normalized on April 13. She was dischanged on April 28, 2001. The muscle weakness and numbness improved at this time, and had almost completely disappeared in June 2001.

Discussion

This report has described a patient with SLE who developed congestive heart failure and axonal polyneuropathy after 9 months of treatment with alfacalcidol for the prevention of corticosteroid-induced osteoporosis. The serological data did not show any evidence of an exacerbation of SLE when the patient developed congestive heart failure and axonal polyneuropathy. In addition, after the discontinuation of alfacalcidol, both congestive heart failure and axonal polyneuropathy improved without an increase in the dose of prednisolone. It is therefore most likely that both congestive heart failure and axonal polyneuropathy were the result of the toxic effects of alfacalcidol. Of course, it is still possible that the presence of SLE itself might be related to the development of the toxic effects of alfacalcidol, although the precise mechanisms remain to be elucidated.

It is noteworthy that it required a longer time for the patient to recover from axonal polyneuropathy than from congestive heart failure. Thus, when the patient began to recover from congestive heart failure on March 13, she still



WBC(/μl)	2700	7000	7400	6800	7200	7300
Hb(g/dl)	9.8	11.7	13.6	14.4	13.6	13.8
Plt(/μl)	17.8	19.9	22.3	23.1	24.0	22.5
Anti-DNA(IU/ml)	290	25.9	18.7	19.5	16.3	10.5
I.C.(μgEq/ml)	10.2	2.7	1.4	1.8	2.1	2.3
C3(mg/dl)	60	77	79	80	89	78
C4(mg/dl)	11	12	13	13	15	11
ANA	x 2560	x 160	x 40	x 40	x 40	x 40

Fig. 2. Clinical course of the patient. No evidence of an exacerbation of SLE was found when the patient developed congestive heart failure and numbness. *IC*, immune complex; *ANA*, antinuclear antibody

suffered from numbness and muscle weakness. In addition, our patient did not show any evidence of the presence of Sjögren's syndrome, antiphospholipid antibody syndrome, or vasculitis syndrome, which can also lead to axonal neuropathy.[6–9] Moreover, serum antigangliodise antibody was negative in our patient, thus obviating the possibility that the patient had any of a variety of autoimmune neuropathies.[10,11]

Therefore, it is most likely that the axonal polyneuropathy in our patient was caused by alfacalcidol. It appears that the mechanisms of damage by alfacalcidol might differ depending on the tissues involved. Alfacalcidol has commonly been used in the prevention of corticosteroid-induced osteoporosis in various rheumatic diseases.[4,5] Although mild toxic effects, such as gastrointestinal symptoms, liver dysfunction, renal dysfunction, ectopic calcification, and hypercalcemia, are occasionally observed, serious life-threatening side-effects, such as congestive heart failure or severe axonal neuropathy, have not been reported. Since corticosteroid-induced osteoporosis is a very common problem in the management of rheumatic diseases, rheumatologists should be aware of the possibility of the life-threatening toxic effects of alfacalcidol.

The precise mechanisms of the development of congestive heart failure and axonal neuropathy in our patient are currently unclear. Recent studies have demonstrated the presence of vitamin D receptor in the human heart[12] as well as in murine peripheral nerves,[13] indicating that vitamin D affects these tissues. It is likely that vitamin D resulted in congestive heart failure and peripheral neuropathy in our patient through direct toxic actions on the heart as well as on peripheral nerves. Although the mechanism of toxicity remains unclear, it may well be related to some polymorphism of vitamin D receptor genes. It is important to remember that our patient has SLE. Since vitamin D receptor is expressed on immune competent cells, such as T cells and monocytes,[14] it is also possible that vitamin D might result in damage to the heart and peripheral nerves through undermined immunological mechanisms that are related to SLE. Further studies are required to delineate the mechanism of toxicity of vitamin D in SLE patients.

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